(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
7 December 2000 (07.12.2000)

PCT

(10) International Publication Number
WO 00/73313 A1

(51) International Patent Classification[7]: C07D 495/04, 498/04, 233/20, A61K 31/55, 31/395, 31/553, 31/554, A61P 9/00, 19/00, 25/00

(21) International Application Number: PCT/SE00/01034

(22) International Filing Date: 23 May 2000 (23.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
9901901-0 26 May 1999 (26.05.1999) SE

(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MATZ, James [US/US]; 60 Waterford Way, Fairport, NY 14450 (US). MCDONALD, James [US/US]; Trega Biosciences, 9880 Campus Point Drive, San Diego, CA 92121 (US). WU, Edwin [US/US]; 147 Ashley Drive, Rochester, NY 14620 (US).

(74) Agent: ASTRAZENECA AB; Global Intellectual Property, Patents, S-151 85 Södertälje (SE).

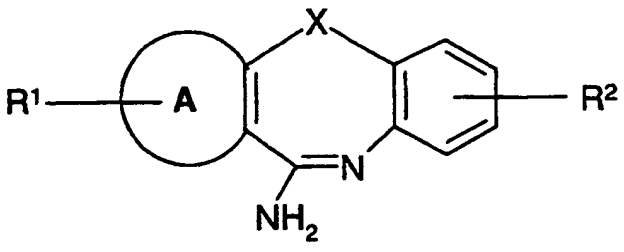
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW TRICYCLIC AMIDINE DERIVATIVES AS INHIBITORS OF NITRIC OXIDE SYNTHASE



(I)

(57) Abstract: There are provided novel compounds of formula (I), wherein R^1, R^2, A and X are as defined in the specification, and optical isomers, racemates and tautomers thereof and pharmaceutically acceptable salts thereof; together with processes for their preparation, compositions containing them and their use in therapy. The compounds are inhibitors of the enzyme nitric oxide synthase.

WO 00/73313 A1

NEW TRICYCLIC AMIDINE DERIVATIVES AS INHIBITORS OF NITRIC OXIDE SYNTHASE

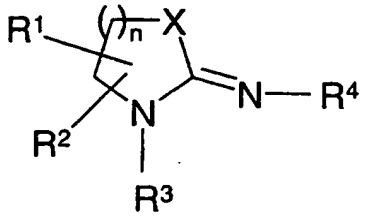
Field of the Invention

This invention relates to new tricyclic amidine derivatives, processes for their preparation, compositions containing them and their use in therapy.

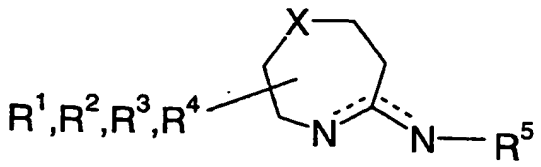
Background of the Invention

Nitric oxide is produced in mammalian cells from L-arginine by the action of specific nitric oxide synthases (NOSs). These enzymes fall into two distinct classes - constitutive NOS (cNOS) and inducible NOS (iNOS). At the present time, two constitutive NOSs and one inducible NOS have been identified. Of the constitutive NOSs, an endothelial enzyme (ecNOS) is involved with smooth muscle relaxation and the regulation of blood pressure and blood flow, whereas the neuronal enzyme (ncNOS) serves as a neurotransmitter and appears to be involved in the regulation of various biological functions such as cerebral ischaemia. Inducible NOS has been implicated in the pathogenesis of inflammatory diseases. Specific regulation of these enzymes should therefore offer considerable potential in the treatment of a wide variety of disease states.

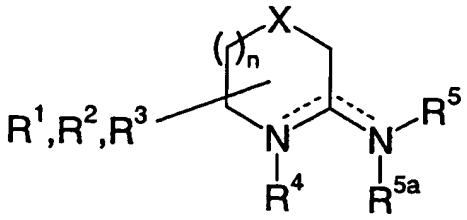
Considerable effort has been expended in efforts to identify compounds that act as specific inhibitors of one or more isoforms of the enzyme nitric oxide synthase. The use of such compounds in therapy has also been widely claimed. One group of these compounds features within their structures a cyclic amidine moiety. Thus, WO 95/11231 (G.D. Searle & Co.) discloses compounds of general formula:



and WO 97/16430 and US 5,629,322 (both to Merck & Co., Inc.) describe cyclic amidines of general formula:

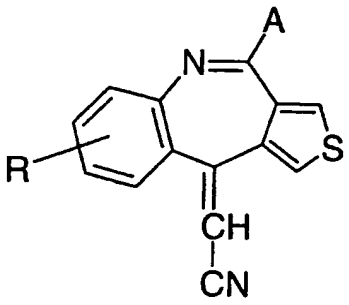


and



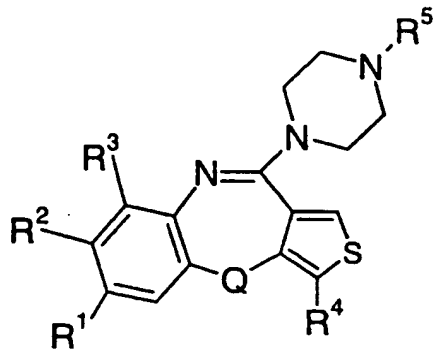
respectively.

Certain tricyclic structures which incorporate a cyclic amidine moiety are also known. Thus, US 4,745,111 (BASF AG) discloses 4-substituted 10-cyanomethylenethieno[4,3-e]benzoazepines of general formula



which compounds are claimed to be useful in the treatment of agitation, anxiety and sleepless states.

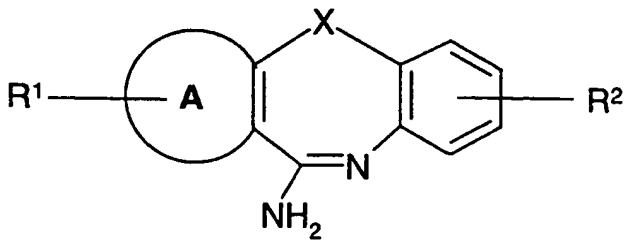
US 4,157,444 (American Cyanamid Co.) describes 10-(1-piperazinyl)thieno[3,4-b][1,5]-benzoxazepines and -benzothiazepines of general formula



which display neuroleptic activity.

Disclosure of the Invention

According to the invention we provide a compound of formula (I)



(I)

wherein:

R^1 represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy or halogen;

R^2 represents hydrogen or a group $-Z-R^3$;

Z represents a bond or C1 to 8 alkyl;

R^3 represents $-OR^4$, $-CH(OR^4)R^{13}$, $-COR^{14}$, $-CO_2R^5$, $-CONR^6R^7$, -CN, halogen, $-NR^8R^9$ or $-NHC(=NH)-R^{10}$;

X represents CH_2, O, $S(O)_m$, CO, $CHOR^{12}$, CH–halogen, $CHNH_2$, $(CH_2)_2$, CH_2O, OCH_2, CH_2S or SCH_2;

m represents an integer 0, 1 or 2;

A represents a heterocyclic ring containing one heteroatom atom selected from O, S and N;

R^4, R^5, R^6, R^7, R^8, R^9 and R^{12} independently represent hydrogen or C1 to 6 alkyl or unsaturated C2 to 6 alkyl; said alkyl or unsaturated alkyl group being optionally further substituted by one or more groups selected from halogen, –CN, $-CONH_2$ or phenyl; said phenyl being optionally further substituted by C1 to 6 alkyl, C1 to 6 alkoxy or halogen;

R^{10} represents a five membered heterocyclic ring containing one heteroatom selected from O, S and N;

or the groups $-NR^6R^7$ and $-NR^8R^9$ independently represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; said piperazinyl ring being optionally 4-substituted by C1 to 6 alkyl, $-COR^{15}$ or a five or six membered heterocyclic ring containing one heteroatom atom selected from O, S and N; said alkyl group being optionally substituted by phenyl;

R^{13} represents C1 to 6 alkyl;

R^{14} represents hydrogen or C1 to 6 alkyl;

R^{15} represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy or phenyl–C1 to 6 alkoxy;

and optical isomers, racemates and tautomers thereof and pharmaceutically acceptable salts thereof.

Preferably X represents CH_2, O, $S(O)_m$ or $(CH_2)_2$.

More preferably X represents CH_2.

In another preferred embodiment, X represents $S(O)_m$.

Preferably m represents the integer 0.

Preferably A represents a five or six membered heterocyclic ring containing one heteroatom atom selected from O, S and N.

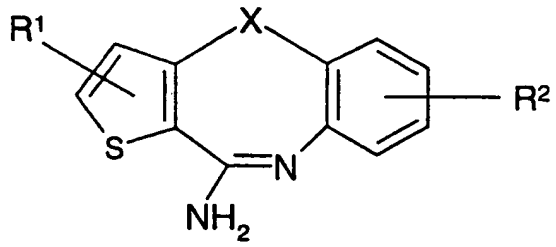
More preferably A represents a five membered heterocyclic ring containing one heteroatom atom selected from O, S and N.

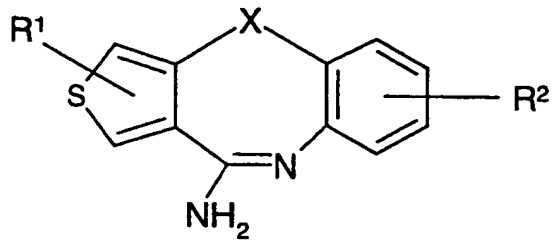
In a particularly preferred embodiment, A represents a thienyl ring.

Preferably Z represents C1 to 4 alkyl. More preferably, –Z– represents $-CH_2-$.

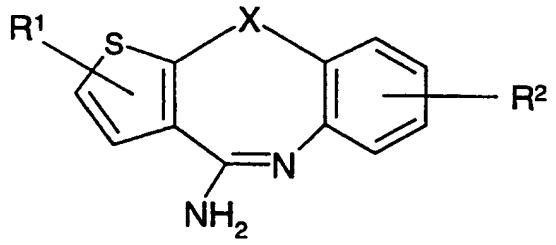
Preferably R^3 represents $-NR^8R^9$.

Examples of compounds wherein A represents a thienyl ring are:





and



Particular compounds of the invention include:

thieno[3,2-b][1,5]benzothiazepin-10-amine;

4H-thieno[2,3-c][1]benzazepin-10-amine;

4,5-dihydrothieno[3,2-c][1]benzazocin-11-amine;

thieno[2,3-b][1,5]benzothiazepin-4-amine;

10H-thieno[3,2-c][1]benzazepin-4-amine;

4H-thieno[3,2-c][1,6]benzothiazocin-11-amine;

thieno[3,2-b][1,5]benzoxazepin-10-amine;

4H-thieno[2,3-c][1]benzazepin-7,10-diamine;

N-(10-amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-2-carboximidamide;

N-(10-amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-3-carboximidamide;

7-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-azetidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-pyrrolidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(N,N-diethylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

methyl 10-amino-4H-thieno[2,3-c][1]benzazepin-7-carboxylate;

10-amino-4H-thieno[2,3-c][1]benzazepin-7-carboxamide;

7-(1-pyrrolidinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-ethanone)-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-hydroxyethyl)- 4H-thieno[2,3-c][1]benzazepin-10-amine;

6-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

thieno[3,4-b][1,5]benzothiazepin-10-amine;

4-oxothieno[3,4-b][1,5]benzothiazepin-10-amine;

10-oxothieno[3,2-c][1]benzazepin-4-amine;

10-hydroxy-10H-thieno[3,2-c][1]benzazepin-4-amine;

4H-thieno[2,3-c][1]benzazepin-4,10-diamine;

4-oxothieno[2,3-c][1]benzazepin-10-amine;

4-hydroxy-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(cyclopropylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-cyano-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-aminocarbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

4-chloro-4H-thieno[2,3-c][1]benzazepin-10-amine;

4-ethoxy-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-aminomethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

ethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate;

2-methylethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate;

7-(4-methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-(4-methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

thieno[2,3b][1,5]benzothiazepin-4,9-diamine;

9-cyano-thieno[2,3b][1,5]benzothiazepin-4-amine;

9-chloro-thieno[2,3b][1,5]benzothiazepin-4-amine;

6-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-(4-carbobenzyloxypiperazinyl)carbonyl-4H-thieno[2,3c][1]benzazepin-10-amine;
7-[(4-methylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(4-morpholinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(N-methyl-N-propylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(4-(2-pyridinyl)piperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(4-carbethoxypiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(4-acetylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[N-(2-fluoroethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
7-[(methylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
6-[(N,N-dimethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;
ethyl 4-amino-10H-thieno[3,2-c][1]benzazepine-7-carboxylate;
7-hydroxymethyl-4H-thieno[3,2-c][1]benzazepin-4-amine;
7-(chloromethyl)-10H-thieno[3,2-c][1]benzazepin-4-amine;
7-[(isopropylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;
7-[(ethylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;
6-{[(4-methoxybenzyl)amino]methyl}-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;
[[(10-amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetonitrile;
2-[[(10-amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetamide;
and pharmaceutically acceptable salts thereof.

Unless otherwise indicated, the term "C1 to 6 alkyl" referred to herein denotes a straight or branched chain alkyl group having from 1 to 6 carbon atoms or a cyclic alkyl group having from 3 to 6 carbon atoms. Examples of such groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, cyclopentyl and cyclohexyl.

The term "C1 to 8 alkyl" is to be interpreted analogously.

Unless otherwise indicated, the term "C2 to 6 unsaturated alkyl" referred to herein denotes a straight or branched chain alkyl group having from 2 to 6 carbon atoms and including one double bond or one triple bond or a cyclic alkyl group having from 3 to 6 carbon atoms and including one double bond. Examples of such groups include ethenyl, ethynyl,

1- and 2-propenyl, 1- and 2-propynyl, 2-methyl-2-propenyl, 2-butenyl, 2-butynyl, cyclopentenyl and cyclohexenyl.

Unless otherwise indicated, the term "C1 to 6 alkoxy " referred to herein denotes a straight or branched chain alkoxy group having from 1 to 6 carbon atoms. Examples of such groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, i-butoxy, s-butoxy and t-butoxy.

Unless otherwise indicated, the term "halogen" referred to herein denotes fluorine, chlorine, bromine and iodine.

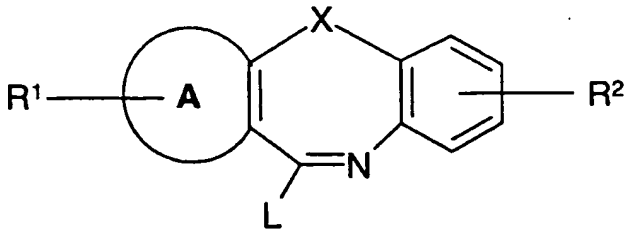
Examples of a "phenyl–C1 to 6 alkoxy" group include benzyloxy and phenethyloxy.

Examples of a five or six membered heterocyclic ring containing one heteroatom selected from O, S and N include furan, thiophene, pyrrole and pyridine.

The present invention includes compounds of formula (I) in the form of salts, in particular acid addition salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable acids may be of utility in the preparation and purification of the compound in question. Thus, preferred salts include those formed from hydrochloric, hydrobromic, sulphuric, phosphoric, citric, tartaric, lactic, pyruvic, acetic, succinic, fumaric, maleic, methanesulphonic and benzenesulphonic acids.

According to the invention, we further provide a process for the preparation of compounds of formula (I), and optical isomers and racemates thereof and pharmaceutically acceptable salts thereof, which comprises:

(a) preparing a compound of formula (I) by reacting a corresponding compound of formula (II)

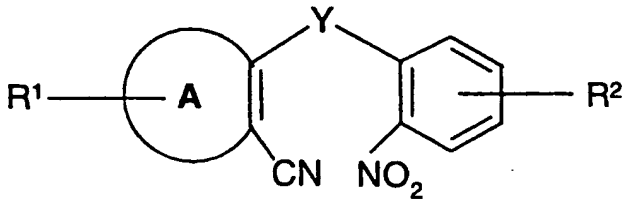


(II)

wherein R^1, R^2, A and X are as defined above and L is a leaving group,

with a source of $-NH_2$ such as ammonia or ammonium acetate;

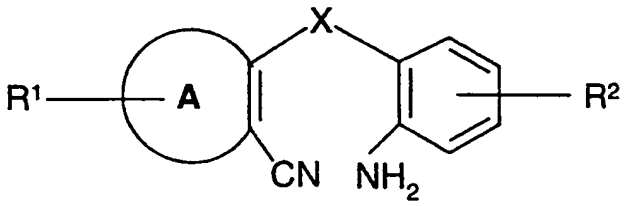
(b) preparing a compound of formula (I) by reduction and cyclisation of a corresponding compound of formula (III)



(III)

wherein R^1, R^2 and A are as defined above, and Y represents X (which is as defined above) or $CHSO_2C_6H_4CH_3$;

(c) preparing a compound of formula (I) by cyclisation of a corresponding compound of formula (IV)



(IV)

wherein R^1, R^2, A and X are as defined above;

(d) preparing a compound of formula (I) wherein R^2 represents $-Z-CH_2-NR^8R^9$ by reductive amination of a corresponding compound of formula (I) wherein R^2 represents

–Z–CHO;

(e) preparing a compound of formula (I) wherein R^2 represents –Z–NR^8R^9 by amination of a corresponding compound of formula (I) wherein R^2 represents –Z–L´ and L´ is a leaving group;

(f) preparing a compound of formula (I) wherein X represents C=O by oxidation of a corresponding compound of formula (I) wherein X represents CH_2;

(g) preparing a compound of formula (I) wherein X represents CHOH by reduction of a corresponding compound of formula (I) wherein X represents C=O;

(h) preparing a compound of formula (I) wherein X represents $CHNH_2$ by converting a compound of formula (I) wherein X represents CHOH into the corresponding azide wherein X represents CHN_3, followed by reduction;

(i) preparing a compound of formula (I) wherein X represents $S(O)_m$ and m represents 1 or 2, by oxidation of a corresponding compound wherein X represents $S(O)_m$ and m represents 0;

(j) preparing a compound of formula (I) wherein R^2 represents –Z–$CONR^6R^7$ or –Z–CO_2R^5 by oxidation of the corresponding compound wherein R^2 represents –Z–CHO;

(k) preparing a compound of formula (I) wherein R^2 represents –Z–$CONH_2$ or –Z–CO_2R^5 by solvolysis of the corresponding compound wherein R^2 represents –Z–CN;

or

(l) preparing a compound of formula (I) wherein X represents $CHOR^{12}$ by solvolysis of the corresponding compound wherein X represents CH–halogen;

and where necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or vice versa, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

In process (a), the reaction may be performed by combining the reactants in a polar protic solvent such as methanol, ethanol or propanol, or in a polar aprotic solvent such as N,N-dimethylformamide or N-methyl-2-pyrrolidinone at a temperature from 20 to 100 ^{0}C. The reaction time will depend *inter alia* on the polarity of the solvent, the nature of the leaving group and the temperature of the reaction, and may be up to 2 weeks. However, it will typically be from 2 to 5 days. We prefer, although it is not required, to perform this reaction in the presence of an ammonium salt such as ammonium acetate. Suitable leaving groups L include thioalkyl, sulfonate, trifluoromethylsulfonate, halide, alkoxide, aryloxide and tosylate groups; others are recited in "Advanced Organic Chemistry", J. March (1985) 3rd Edition on page 315 and are well known in the art. We find thioalkyl to be particularly useful. When L represents thioalkyl the process is generally performed in a pressure bottle with methanol as solvent.

In process (b), the reaction is preferably performed by treating a compound of formula (III) in a suitable solvent and in the presence of an acid catalyst with a reducing agent that is capable of effecting the reduction of the aryl nitro group to an aniline. The reducing agent is generally a transition metal such as, but not limited to, zinc, tin or iron. The solvent may be water or a suitable organic solvent, or an organic solvent containing varying concentrations of water. Suitable organic solvents are those such as acetonitrile, dioxane, tetrahydrofuran, N,N-dimethylformamide, and C_1 to C_4 alcohols. The acid catalyst may be an organic or inorganic acid, for instance, hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, lactic, succinic, fumaric, malic, maleic, tartaric, citric, benzoic or methanesulfonic acid. In a particular embodiment, and especially when Y represents

$CHSO_2C_6H_4CH_3$, we prefer that the reducing agent is zinc, the acid catalyst is acetic acid and the reaction is performed neat or admixed with a C1 to 4 alcohol. Under these conditions, reduction of the nitro group occurs and is followed by cyclisation, and also when Y represents the group $CHSO_2C_6H_4CH_3$, this is reduced to CH_2.

In process (c), the cyclization reaction of a compound of formula (IV) will take place when either the neat compound or a solution of the compound in an inert solvent is kept at a suitable temperature, generally between room temperature and 150 °C. The reaction time will vary from 1 day to 4 weeks depending on the actual conditions used. The reaction may be accelerated by the use of either an acid or a base. An example where sodium hydride is the base is described by Y. Mettey *et al.*, J. Heterocycl. Chem., 1997, **34**, 465-467. We prefer the acid variant wherein the compound of formula (IV) is first converted into the corresponding salt using either an inorganic or organic acid such as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, lactic, succinic, fumaric, malic, maleic, tartaric, citric, benzoic or methanesulfonic acid, and the salt is then heated at a temperature from 100 to 300 °C for between 0.01 to 5 h, with heating to 150 to 200 °C for about 0.1 to 1 h being preferred.

In process (d), the reductive amination reaction generally takes place under conditions which will be known to persons skilled in the art. For example, treatment of an aldehyde with an amine in the presence of a reducing agent in an inert solvent. Suitable reducing systems include catalytic hydrogenation or borane and derivatives thereof. A partial list of such reagents can be found in "Advanced Organic Chemistry", J. March (1985) 3rd Edition on page 799.

In process (e), the amination reaction is performed by reacting a compound of formula (I) wherein R^2 represents $-Z-L'$ and L' is a leaving group with an amine in an inert solvent. Suitable leaving groups include sulfonate, trifluorosulfonate, tosylate, and halides selected from the group chloride, bromide or iodide. The nucleophile can be a primary or secondary amine in the presence of a base. This base can be either an excess of the amine

nucleophile or can be an additive to the reaction mixture. Potential basic additives are metal carbonate, especially alkali metal carbonates, metal oxides and hydroxides, and tertiary amine bases. Suitable organic solvents are those such as acetonitrile, dioxane, N,N-dimethylformamide, N-methyl-2-pyrrolidinone, tetrahydrofuran, dimethylsulfoxide, sulfolane and C1 to 4 alcohols. In a preferred embodiment, the leaving group is chloride, the amine is used in a 2 to 20 fold excess, and the solvent is N-methyl-2-pyrrolidinone.

In process (f), the oxidation is performed by combining the reactants is an inert halogenated solvent such as chloroform or methylene chloride or in an inert solvent such as N,N-dimethylformamide or N-methyl-2-pyrrolidinone, either alone or admixed with water, at a temperature range from 20 to 100 °C. The reaction time will depend on the nature of the oxidant and the temperature of the reaction and may be up to a week; however it will be typically from 1 to 12 hours. Suitable oxidants include activated manganese dioxide, chromyl chloride, and various cerium (III) salts such as ceric ammonium nitrate and ceric trifluoroacetate. In a preferred embodiment, the oxidation is performed by refluxing a solution of a compound of formula (I) wherein X represents CH_2 in chloroform using activated manganese dioxide as the oxidizing reagent for 1 to 5 hours.

In process (g), the reduction is performed by treating a compound of formula (I), wherein X represents C=O, and generally takes place under conditions which will be known to persons skilled in the art. For example, treatment of the ketone in an inert solvent in the presence of a reducing agent. Suitable reducing agents include aluminium hydrides and borohydrides including hydride salt forms of these, isopropyl alcohol in combination with aluminium isopropoxide, and alkali metal in alcoholic solvents such as sodium in ethanol. A partial list of suitable reducing agents can be found in "Advanced Organic Chemistry", J. March (1985) 3rd Edition on pages 809-814. The preferred solvents for this process are acyclic ethers, such as diethyl ether and dimethoxyethane, and cyclic ethers, such as tetrahydrofuran and dioxane when reactive hydride reagents such as lithium aluminium hydride or complex borohydrides, such as lithium or potassium tri-sec-butylborohydride, are used as the reducing agents. When less reactive reducing reagents such as sodium

borohydride for example are used, C1 to 4 alcohols at ambient temperatures are preferred as solvents.

In process (h), a two step conversion is involved. Firstly, the alcohol is converted into the corresponding azide by treatment with an azide salt in the presence of a strong acid, and then the azide is reduced to the corresponding amine. The azide salt is preferably, but not limited to, an alkali metal azide such as sodium azide. This reaction may be performed using the acid as solvent or in the presence of an inert solvent such as halocarbons, ethers, or alkanes using either a mineral acid, such as sulfuric acid, hydrogen chloride or hydrogen bromide, or a strong organic acid such as benzenesulfonic,acid, trifluoroacetic acid or triflic acid, at low to ambient temperatures. The azide salt can be added directly or can be introduced on a support such as, for example, a zeolite. The azide product can be isolated or taken directly on to the reduction step. Suitable reducing agents can be selected from the group, hydrogen using a noble metal catalyst, Raney nickel and phosphorous compounds such as triphenylphosphine , tributylphosphine or triethylphosphite, in water or in C1 to 4 alcohols either alone or diluted with water. In a preferred embodiment, the alcohol in trifluoroacetic acid is treated with sodium azide at ambient temperature. The reaction mixture is diluted with aqueous alcohol and treated with hydrogen in the presence of palladium on carbon.

In process (i), the process is performed by reacting a compound of formula (I) wherein X is S with a suitable oxidizing agent in an inert solvent. The reaction can be controlled so as to afford either the corresponding sulfoxide (X = SO) or sulfone ($X = SO_2$) by correct choice of the oxidizing reagent used, the quantity of reagent used and the reaction conditions employed. Suitable oxidizing reagents and reaction conditions are given in "Advanced Organic Chemistry", J. March (1985) 3rd Edition on page 1089-1090.

In process (j), the reaction is preferably performed by treating a compound of formula (I) wherein R^2 represents –Z–CHO with either an amine or an alcohol in the presence of a metal cyanide salt and an oxidizing agent at ambient temperature. In the case where an

ester is to be formed, it is convenient but not necessary to use the alcohol as the solvent for this process. In the case where an amide is to be formed, it is necessary to use a less reactive secondary alcohol, such as sec-butanol or isopropanol, or a tertiary alcohol like tert-butanol as the solvent. The reaction may be diluted with other inert aprotic, polar solvents such as acetonitrile or N,N-dimethylformamide. The reaction is generally performed at ambient temperature for from 1 to 24 h depending on the nature of the alcohol and amine and the solubility of the metal cyanide. Manganese dioxide is the preferred oxidizing reagent for this process.

In process (k), the reaction may be performed by mixing the nitrile with an alcohol in the presence of an acid catalyst at a suitable temperature. Conversely, this process may also be accomplished by dissolving the nitrile in a neat strong organic or inorganic acid such as sulfuric, methanesulfonic, or triflic acids, and then pouring the mixture into an aqueous or alcoholic solution. In preferred embodiments, esters are formed by the former method, whereas the primary amides are prepared using the latter method with sulfuric acid as the acid catalyst and pouring over ice as a convenient source of cooling and water.

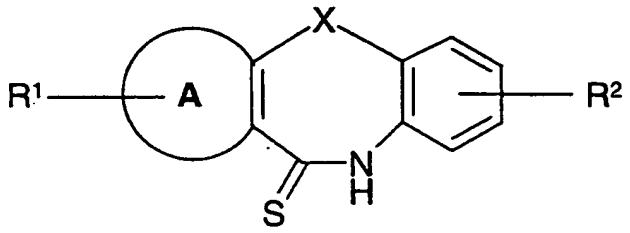
In process (l), the solvolysis reaction is performed by stirring a solution of the corresponding halo derivative, preferably the chloro derivative, in the appropriate alcohol solvent ($R^{12}OH$) at a suitable temperature. The solvent can be either neat or admixed with a polar, inert solvent such as acetonitrile, sulfolane, N,N-dimethylformamide or tetrahydrofuran. In a preferred embodiment, the chloro derivative is added to the neat alcohol at ambient temperature.

Salts of compounds of formula (I) may be formed by reacting the free base or a salt, enantiomer, tautomer or protected derivative thereof, with one or more equivalents of the appropriate acid. The reaction may be carried out in a solvent or medium in which the salt is insoluble, or in a solvent in which the salt is soluble followed by subsequent removal of the solvent in vacuo or by freeze drying. Suitable solvents include, for example, water,

dioxan, ethanol, 2-propanol, tetrahydrofuran or diethyl ether, or mixtures thereof. The reaction may be a metathetical process or it may be carried out on an ion exchange resin.

Compounds of formula (II) may be prepared by methods which will be generally known, for example by reference to M. Lora-Tamayo *et al.*, Tetrahedron, 1966, Suppl. **8**, 305-312; M. W. Gittos *et al.*, J. Chem. Soc. Perkin Trans. I, 1976, 33-38; and G. D. Diana *et al.*, J. Med. Chem., 1977, **20**, 449-452. These methods include the formation of thioalkyl derivatives of formula (II) by cyclization of an isothiocyanate, and the formation of an iminoester derivative of formula (II) by treatment of the corresponding cyclic amide with Meerwein's reagent (triethyloxonium tetrafluoroborate). The isothiocyanate and iminoester precursors may be readily prepared by methods that are also disclosed or cited in these papers, or by conventional methods known *per se*.

Alternatively, compounds of formula (II) in which L represents thioalkyl may be readily prepared by treatment of a compound of formula (V)



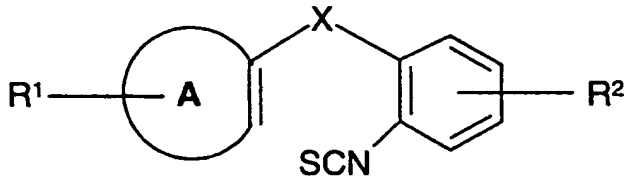
(V)

wherein A, R^1, R^2 and X are as defined above,

with an alkylating agent such as an alkyl tosylate, methosulfate, mesylate, fluorosulphonate or halide, especially an alkyl iodide. Suitable solvents for the alkylation reaction include ethers, preferably diethyl ether, tetrahydrofuran or dioxane, lower ketones such as acetone or 2-butanone, halohydrocarbons such as dichloromethane and lower alcohols such as methanol. Use of methyl iodide as the alkylating agent and acetone as the solvent is a particularly suitable combination. Generally, equimolar or an excess of the alkylating agent will be used, the amount depending *inter alia* on the reactivity of the compound of

formula (V) and the solubility of the reactants in the solvent employed. The alkylation reaction may be carried out at temperatures ranging from ambient to reflux, or in an appropriate sealed vessel at higher temperature.

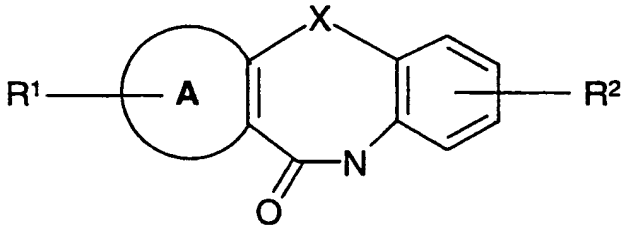
Compounds of formula (V) may be prepared by ring closure of a corresponding compound of formula (VI)



(VI)

wherein A, R^1, R^2 and X are as defined above. The reaction may be performed using conditions analogous to those described in the above paper by Gittos *et al.*

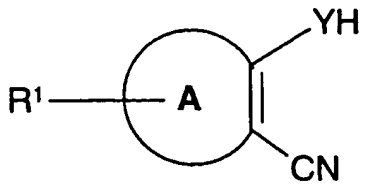
Compounds of formula V may also be prepared from a compound of formula (VII)



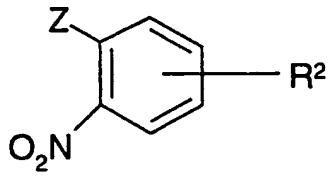
(VII)

wherein A, R^1, R^2 and X are as defined above,
by treatment with P_2S_5 or Lawesson's reagent. Conditions for this reaction and details of alternative sulfur containing reagents may be obtained by reference to the paper by D. C. Smith *et al.*, J. Org. Chem., 1994, **59**, 348-354.

Compounds of formula (III) may be prepared by the reaction together of compounds of formulae (VIII) and (IX)



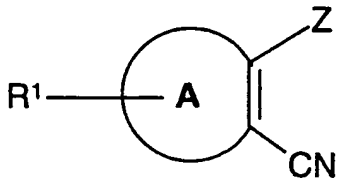
(VIII)



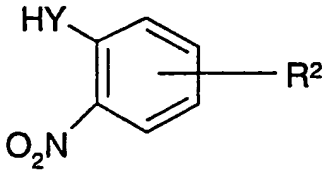
(IX)

wherein A, R^1, R^2, and Y are as defined above, and Z represents a halogen, particularly fluoride or chloride. The reaction may be performed by adding a strong base to a mixture of the compounds of formulae (VIII) and (IX) in an appropriate solvent at a temperature generally between 0 °C and the reflux temperature of the solvent. Examples of suitable bases include alkali metal and tetraalkylammonium hydroxides such as alkali metal alkoxides of C_1 to C_4 alcohols, guanidine and N-substituted guanidines, sodium hydride and dimsyl sodium, with sodium hydroxide and potassium t-butoxide being particularly useful. Suitable solvents include dimethylsulfoxide, N,N-dimethylformamide, tetrahydrofuran, C_1 to C_4 alcohols and acetonitrile, either alone or admixed with water. We find that aqueous sodium hydroxide in dimethylsulfoxide is a particularly suitable reagent.

Alternatively, compounds of formula (III) may be prepared by the reaction together of compounds of formulae (X) and (XI)



(X)

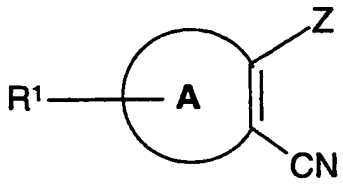


(XI)

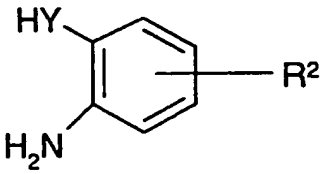
wherein A, R^1, R^2, Y and Z are as defined above, using reaction conditions similar to those described above.

Compounds of formula (IV) may be prepared by the reduction of a compound of formula (III). The reduction may be performed under various conditions such as those described in "Advanced Organic Chemistry", J. March (1985) 3rd Edition on page 1103-1104. These include catalytic hydrogenation, use of zinc, tin, or iron metals, AlH_3-$AlCl_3$, sulfides and others. We prefer to perform the reaction by reduction with zinc in the presence of either acetic acid or dilute hydrochloric acid.

Compounds of formula (IV) may also be prepared from compounds of formulae (X) and (XII)



(X)



(XII)

wherein A, R^1, R^2, Y and Z are as defined above. The reaction may be performed using conditions analogous to those described in the paper of Mettey *et al.* referenced above.

Compounds of formulae (VI), (VII), (VIII), (IX), (X), (XI) and (XII) are either known or may be prepared by conventional methods known per se.

Intermediate compounds may be prepared as such or in protected form. In particular amine, aldehyde and ketone groups may be protected. Suitable protecting groups are described in the standard text "Protective Groups in Organic Synthesis", 2nd Edition (1991) by Greene and Wuts. Amine protecting groups which may be mentioned include alkyloxycarbonyl such as t-butyloxycarbonyl, phenylalkyloxycarbonyl such as benzyloxycarbonyl, or trifluoroacetate. Deprotection will normally take place on treatment

with aqueous base or aqueous acid. Aldehyde and ketone protecting groups which may be mentioned include acetals such as ethylene acetal or dimethyl acetal, or dithioacetals.

The compounds of the invention and intermediates may be isolated from their reaction mixtures, and if necessary further purified, by using standard techniques.

The compounds of formula (I) may exist in tautomeric, enantiomeric or diastereoisomeric forms, all of which are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional techniques, for example, fractional crystallisation or HPLC. Alternatively, the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions that will not cause racemisation.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, diastereomers, racemates or mixtures.

The compounds of formula (I), and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers, are useful because they possess pharmacological activity in animals. In particular, the compounds are active as inhibitors of the enzyme nitric oxide synthase and as such are predicted to be useful in therapy. More particularly, they are inhibitors of the neuronal isoform of the enzyme nitric oxide synthase. They may also have utility as inhibitors of the inducible isoform of the enzyme nitric oxide synthase present in many cell types, particularly macrophages.

The compounds and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers are indicated for use in the treatment or prophylaxis of diseases or conditions in which synthesis or oversynthesis of nitric oxide synthase forms a contributory part.

Examples of such diseases or conditions include hypoxia, such as in cases of cardiac arrest, stroke and neonatal hypoxia, neurodegenerative conditions including nerve degeneration and/or nerve necrosis in disorders such as ischaemia, hypoxia, hypoglycemia, epilepsy, and

in external wounds (such as spinal cord and head injury), hyperbaric oxygen convulsions and toxicity, dementia, for example, pre-senile dementia, Alzheimer's disease and AIDS-related dementia, Sydenham's chorea, Parkinson's disease, Huntington's disease, multiple sclerosis, Amyotrophic Lateral Sclerosis, Korsakoff's disease, imbecility relating to a cerebral vessel disorder, sleeping disorders, schizophrenia, anxiety, depression, seasonal affective disorder, jet-lag, depression or other symptoms associated with Premenstrual Syndrome (PMS), anxiety and septic shock.

The compounds of formula (I) are also useful in the treatment and alleviation of acute or persistent inflammatory or neuropathic pain, or pain of central origin.

The compounds of formula (I) are also useful in the treatment or prophylaxis of inflammation. Conditions that may be specifically mentioned include osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints; eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn; inflammatory eye conditions including uveitis, glaucoma and conjunctivitis; lung disorders in which inflammation is involved, for example, asthma, bronchitis, chronic obstructive pulmonary disease, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome; bacteraemia, endotoxaemia (septic shock), aphthous ulcers, gingivitis, pyresis, pain and pancreatitis; conditions of the gastrointestinal tract including inflammatory bowel disease, Crohn's disease, atrophic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, peptic ulceration, irritable bowel syndrome, reflux oesophagitis, damage to the gastrointestinal tract resulting from infections by, for example, *Helicobacter pylori*, or from treatments with non-steroidal anti-inflammatory drugs; and other conditions associated with inflammation.

The compounds of formula (I) and their pharmaceutically acceptable salts, enantiomers, racemates and tautomers may also be useful in the treatment or prophylaxis of diseases or conditions in addition to those mentioned above. For example, the compounds may be useful in the treatment of atherosclerosis, cystic fibrosis, hypotension associated with septic and/or toxic shock, in the treatment of dysfunction of the immune system, as an adjuvant to short-term immunosuppression in organ transplant therapy, in the treatment of vascular

complications associated with diabetes and in cotherapy with cytokines, for example TNF or interleukins.

Compounds of formula (I) are also predicted to show activity in the prevention and reversal of tolerance to opiates and diazepines, treatment of drug addiction and the treatment of migraine, chronic tension type headaches, cluster headaches and other vascular headaches. The compounds of the present invention may also show useful immunosuppressive activity, and be useful in the treatment of gastrointestinal motility disorders, and in the induction of labour. The compounds may also be useful in the treatment of cancers that express nitric oxide synthase.

Compounds of formula (I) are predicted to be particularly useful in the treatment or prophylaxis of hypoxia or stroke or ischaemia or neurodegenerative conditions or schizophrenia or of migraine, chronic tension type headaches, cluster headaches and other vascular headaches or inflammation or for the treatment of pain. We are particularly interested in the conditions selected from the group consisting of hypoxia, ischaemia, stroke, pain, anxiety, schizophrenia, Parkinson's disease, Huntington's disease, migraine, chronic tension type headaches, cluster headaches and other vascular headaches, rheumatoid arthritis, osteoarthritis and inflammatory bowel disease.

For the treatment of Parkinson's disease, the compounds of formula (I) are expected to be particularly useful either alone, or in combination with other agents such as L-Dopa.

For the treatment of migraine, chronic tension type headaches, cluster headaches and other vascular headaches, the compounds of formula (I) are expected to be particularly useful either alone, or in combination with other agents, particularly in combination with a $5HT_{1B/1D}$ (serotonin-1B/1D) agonist. Thus, the compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a $5HT_{1B/1D}$ (serotonin-1B/1D) agonist or a pharmaceutically acceptable derivative thereof. Particularly preferred $5HT_{1B/1D}$ (serotonin-1B/1D) agonists include sumatriptan, naratriptan, rizatriptan, zolmitriptan, almotriptan, eletriptan and frovatriptan.

Zolmitriptan is especially preferred. The NOS inhibitor and the $5HT_{1B/1D}$ (serotonin-1B/1D) agonist may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

Prophylaxis is expected to be particularly relevant to the treatment of persons who have suffered a previous episode of, or are otherwise considered to be at increased risk of, the disease or condition in question. Persons at risk of developing a particular disease or condition generally include those having a family history of the disease or condition, or those who have been identified by genetic testing or screening to be particularly susceptible to developing the disease or condition.

Thus according to a further aspect of the invention we provide a compound of formula (I), or an optical isomer or racemate thereof or a pharmaceutically acceptable salt thereof, for use as a medicament.

According to another feature of the invention we provide the use of a compound of formula (I) or an optical isomer or racemate thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of the aforementioned diseases or conditions; and a method of treatment or prophylaxis of one of the aforementioned diseases or conditions which comprises administering a therapeutically effective amount of a compound of formula (I), or an optical isomer or racemate thereof or a pharmaceutically acceptable salt thereof, to a person suffering from or susceptible to such a disease or condition.

For the above mentioned therapeutic indications, the dosage administered will, of course, vary with the compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compounds are administered to a human at a daily dosage of between 0.5 mg and 2000 mg (measured as the active ingredient) per day, particularly at a daily dosage of between 2 mg and 500 mg.

The compounds of formula (I), and optical isomers and racemates thereof and pharmaceutically acceptable salts thereof, may be used on their own, or in the form of appropriate medicinal formulations. Administration may be by, but is not limited to, enteral (including oral, sublingual or rectal), intranasal, or topical or other parenteral routes. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

According to the invention, there is provided a pharmaceutical formulation comprising preferably less than 95% by weight and more preferably less than 50% by weight of a compound of formula (I), or an optical isomer or racemate thereof or a pharmaceutically acceptable salt thereof, in admixture with a pharmaceutically acceptable diluent or carrier. The formulation may optionally also contain a second pharmacologically active ingredient such as L-Dopa or a $5HT_{1B/1D}$ agonist.

The compounds of formula (I), and pharmaceutically acceptable derivatives thereof, may also be advantageously used in combination with a COX-2 inhibitor. Particularly preferred COX-2 inhibitors are Celecoxib and MK-966. The NOS inhibitor and the COX-2 inhibitor may either be formulated together within the same pharmaceutical composition for administration in a single dosage unit, or each component may be individually formulated such that separate dosages may be administered either simultaneously or sequentially.

We also provide a method of preparation of such pharmaceutical formulations which comprises mixing the ingredients.

Examples of such diluents and carriers are: for tablets and dragees: lactose, starch, talc, stearic acid; for capsules: tartaric acid or lactose; for injectable solutions: water, alcohols, glycerin, vegetable oils; for suppositories: natural or hardened oils or waxes.

Compositions in a form suitable for oral, that is oesophageal, administration include: tablets, capsules and dragees; sustained release compositions include those in which the

active ingredient is bound to an ion exchange resin which is optionally coated with a diffusion barrier to modify the release properties of the resin.

The enzyme nitric oxide synthase has a number of isoforms and compounds of formula (I), and optical isomers and racemates thereof and pharmaceutically acceptable salts thereof, may be screened for nitric oxide synthase inhibiting activity by following procedures based on those of Bredt and Snyder in *Proc. Natl. Acad. Sci.*, 1990, **87**, 682-685. Nitric oxide synthase converts ^{3}H-L-arginine into ^{3}H-L-citrulline which can be separated by cation exchange chromatography and quantified by scintillation counting.

Screen for neuronal nitric oxide synthase inhibiting activity

The enzyme is isolated from rat hippocampus or cerebellum. The cerebellum or hippocampus of a male Sprague-Dawley rat (250-275g) is removed following CO_2 anaesthesia of the animal and decapitation. Cerebellar or hippocampal supernatant is prepared by homogenisation in 50 mM Tris-HCl with 1 mM EDTA buffer (pH 7.2 at 25 °C) and centifugation for 15 minutes at 20,000 g. Residual L-arginine is removed from the supernatant by chromatography through Dowex AG-50W-X8 sodium form and hydrogen form columns successively, and further centrifugation at 1000 g for 30 seconds. For the assay, 25 µl of the final supernatant is added to each of 96 wells (of a 96 well filter plate) containing either 25 µl of an assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, pH 7.4) or 25 µl of test compound in the buffer at 22 °C and 25 µl of complete assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, 1 mM DTT, 100 µM NADPH, 10 µg/ml calmodulin, pH 7.4). Following a 10 minute equilibration period, 25 µl of an L-arginine solution (of concentration 18 µM ^{1}H-L-arginine, 96 nM ^{3}H-L-arginine) is added to each well to initiate the reaction. The reaction is stopped after 10 minutes by addition of 200 µl of a slurry of termination buffer (20 mM HEPES, 2 mM EDTA, pH 5.5) and Dowex AG-50W-X8 200-400 mesh.
Labelled L-citrulline is separated from labelled L-arginine by filtering each filter plate and 75µl of each terminated reaction is added to 3 ml of scintillation cocktail. The L-citrulline is then quantified by scintillation counting.

In a typical experiment using the cerebellar supernatant, basal activity is increased by 20,000 dpm/ml of sample above a reagent blank which has an activity of 7,000 dpm/ml. A reference standard, N-nitro-L-arginine, which gives 80% inhibition of nitric oxide synthase at a concentration of 1 μM, is tested in the assay to verify the procedure.

Screen for human neuronal nitric oxide synthase inhibiting activity

Enzyme was isolated from human hippocampus, cortex or cerebellum. Cerebellar, cortical or hippocampal supernatant is prepared by homogenisation of frozen human tissue (1 to 5 g) in 50 mM Tris-HCl with 1 mM EDTA buffer (pH 7.2 at 25 °C) and centrifugation for 15 minutes at 20,000 g. Residual L-arginine is removed from the supernatant by chromatography through Dowex AG-50W-X8 sodium form and hydrogen form columns successively and further centrifugation at 1000 g for 30 seconds. Subsequently, the supernatant is passed through 2'-5' ADP Sepharose and the human nNOS eluted with NADPH.

For the assay, 25 μl of the final supernatant is added to each of 96 wells (of a 96 well filter plate) containing either 25 μl of an assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, pH 7.4) or 25 μl of test compound in the buffer at 22 °C and 25 μl of complete assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, 1 mM DTT, 100 μM NADPH, 10 μg/ml calmodulin, pH 7.4). Following a 30 minute equilibration period, 25 μl of an L-arginine solution (of concentration 12 μM ^{1}H-L-arginine, 96 nM ^{3}H-L-arginine) is added to each test tube to initiate the reaction. The reaction is stopped after 30 minutes by addition of 200 μl of a slurry of termination buffer (20 mM HEPES, 2 mM EDTA, pH 5.5) and Dowex AG-50W-X8 200-400 mesh.

Labelled L-citrulline is separated from labelled L-arginine by filtering each filter plate and 75 μl of each terminated reaction is added to 3 ml of scintillation cocktail. The L-citrulline is then quantified by scintillation counting.

In a typical experiment using the cerebellar supernatant, basal activity is increased by 20,000 dpm/ml of sample above a reagent blank which has an activity of 7,000 dpm/ml. A reference standard, N-nitro-L-arginine, which gives 80% inhibition of nitric oxide synthase at a concentration of 1 μM, is tested in the assay to verify the procedure.

Screen for human inducible nitric oxide synthase inhibiting activity

Partially purified iNOS was prepared from cultured and lysed human DLD1 cells which had been activated with TNF-alpha, interferon gamma, and LPS. Centrifugation at 1000g removed cellular debris and residual L-arginine was removed from the supernatant by chromatography through Dowex AG-50W-X8 sodium form and hydrogen form columns successively.

For the assay, 25 µl of the final supernatant is added to each of 96 wells (of a 96 well filter plate) containing either 25 µl of an assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, pH 7.4) or 25 µl of test compound in the buffer at 22 °C and 25 µl of complete assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, 1 mM DTT, 100 µM NADPH, 10 µg/ml calmodulin, pH 7.4). Following a 30 minute equilibration period, 25 µl of an L-arginine solution (of concentration 12 µM ^{1}H-L-arginine, 96 nM ^{3}H-L-arginine) is added to each test tube to initiate the reaction. The reaction is stopped after 30 minutes by addition of 200 µl of a slurry of termination buffer (20 mM HEPES, 2 mM EDTA, pH 5.5) and Dowex AG-50W-X8 200-400 mesh.

Labelled L-citrulline is separated from labelled L-arginine by filtering each filter plate and 75 µl of each terminated reaction is added to 3 ml of scintillation cocktail. The L-citrulline is then quantified by scintillation counting.

In a typical experiment using the DLD1 supernatant, basal activity is increased by 10,000 dpm/ml of sample above a reagent blank which has an activity of 5,000 dpm/ml. A reference standard, N-methyl-L-arginine, which gives 80% inhibition of nitric oxide synthase at a concentration of 1 µM, is tested in the assay to verify the procedure.

Screen for endothelial nitric oxide synthase inhibiting activity

The enzyme is isolated from human umbilical vein endothelial cells (HUVECs) by a procedure based on that of Pollock *et al* in *Proc. Natl. Acad. Sci.*, 1991, **88**, 10480-10484. HUVECs were purchased from Clonetics Corp (San Diego, CA, USA) and cultured to confluency. Cells can be maintained to passage 35-40 without significant loss of yield of nitric oxide synthase. When cells reach confluency, they are resuspended in Dulbecco's phosphate buffered saline, centrifuged at 800 rpm for 10 minutes, and the cell pellet is then homogenised in ice-cold 50 mM Tris-HCl, 1 mM EDTA, 10% glycerol, 1 mM

phenylmethylsulphonylfluoride, 2 μM leupeptin at pH 4.2. Following centrifugation at 34,000 rpm for 60 minutes, the pellet is solubilised in the homogenisation buffer which also contains 20 mM CHAPS. After a 30 minute incubation on ice, the suspension is centrifuged at 34,000 rpm for 30 minutes. The resulting supernatant is stored at -80 °C until use.

For the assay, 25 μl of the final supernatant is added to each of 12 test tubes containing 25 μl L-arginine solution (of concentration 12 μM ^{1}H-L-arginine, 64 nM ^{3}H-L-arginine) and either 25 μl of an assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, pH 7.4) or 25 μl of test compound in the buffer at 22 °C. To each test tube was added 25 μl of complete assay buffer (50 mM HEPES, 1 mM EDTA, 1.5 mM $CaCl_2$, 1 mM DTT, 100 μM NADPH, 10 μg/ml calmodulin, 12 μM tetrahydrobiopterin, pH 7.4) to initiate the reaction and the reaction is stopped after 10 minutes by addition of 2 ml of a termination buffer (20 mM HEPES, 2 mM EDTA, pH 5.5).

Labelled L-citrulline is separated from labelled L-arginine by chromatography over a Dowex AG-50W-X8 200-400 mesh column. A 1 ml portion of each terminated reaction mixture is added to an individual 1 ml column and the eluant combined with that from two 1 ml distilled water washes and 16 ml of scintillation cocktail. The L-citrulline is then quantified by scintillation counting.

In a typical experiment, basal activity is increased by 5,000 dpm/ml of sample above a reagent blank which has an activity of 1500 dpm/ml. A reference standard, N-nitro-L-arginine, which gives 70-90% inhibition of nitric oxide synthetase at a concentration of 1 μM, is tested in the assay to verify the procedure.

In the screens for nitric oxide synthase inhibition activity, compound activity is expressed as IC_{50} (the concentration of drug substance that gives 50% enzyme inhibition in the assay). IC_{50} values for test compounds were initially estimated from the inhibiting activity of 1, 10 and 100 μM solutions of the compounds. Compounds that inhibited the enzyme by at least 50% at 10 μM were re-tested using more appropriate concentrations so that an IC_{50} could be determined.

When tested in the above screens, the compounds of Examples 1 to 62 below show IC_{50} values for inhibition of neuronal or inducible nitric oxide synthase of less than 10 μM and good selectivity compared to inhibition of the endothelial isoform of the enzyme, indicating that they are predicted to show particularly useful therapeutic activity.

The invention is illustrated but in no way limited by the following examples:

Example 1

Thieno[3,2-b][1,5]benzothiazepin-10-amine maleate

(a) 10-Methylthiothieno[3,2-b][1,5]benzothiazepine hydroiodide

A suspension of thieno[3,2-b][1,5]benzothiazepin-10-one (3.01 g, 12.9 mmol) (C. Corral *et al.*, J. Heterocycl. Chem., 1985, **22**, 1345-1348) and Lawesson's reagent (2.30 g) in anhydrous tetrahydrofuran (30 ml) was heated at reflux for 4 h. The solvent was removed in vacuum and the residue was purified by chromatography on silica gel using chloroform as eluent to give the crude thioamide. This was immediately taken up in acetone (35 ml) and methyl iodide (4.0 ml) was added and the solution was stirred overnight. The resulting solid was collected to give the title compound (0.58 g, 18%).

^{1}H NMR (d_6-DMSO) 8.6-8.7 (broad, 1H), 7.90 (d, 2H), 7.3-7.4 (m, 2H), 7.19 (d, 2H), 7.11 (d, 1H), 2.60 (s, 3H);

MS (CI) $^m/z$ 264 ($[M+H]^+$, 100%), 216 (10%).

(b) Thieno[3,2-b][1,5]benzothiazepin-10-amine maleate

A pressure bottle containing 10-methylthiothieno[3,2-b][1,5]benzothiazepine hydroiodide (0.55 g, 1.41 mmol) in methanol (10 ml) and ammonium acetate (2.20 g) was heated at 80 °C for 120 h. The reaction mixture was poured into dilute hydrochloric acid and was washed with ethyl acetate. The aqueous phase was basified with dilute aqueous sodium hydroxide and extracted twice with dichloromethane. The dried (magnesium sulfate) organic phases were concentrated to give a yellow solid (0.28 g, 85%). This material was dissolved in 2-propanol (10 ml) and maleic acid (0.21 g) was added. Upon cooling, the

solid was collected to give the title compound (0.38 g, 78%) as a pale yellow solid, m.p. 219.5-220.5 ^{0}C (dec).

Example 2

4H-Thieno[2,3-c][1]benzazepin-10-amine maleate

(a) 10-Methylthio-4H-thieno[2,3-c][1]benzazepine hydroiodide

A suspension of thieno[2,3-c][1]benzazepin-10-one (4.08 g, 19.0 mmol) (F. Hunziker *et al.*, Eur. J. Med. Chem. Chim. Ther., 1981, **16**, 391-398) and Lawesson's reagent (3.37 g, 12.7 mmol) in anhydrous tetrahydrofuran (40 ml) was heated at reflux for 4 h. The solvent was removed in vacuum and the residue was purified by chromatography on silica gel using chloroform as eluent to give the thioamide as a yellow solid. This was immediately taken up in acetone (45 ml) and methyl iodide (4.0 ml) was added and the solution was stirred for 8 h. The resulting solid was collected to give the title compound (4.14 g, 59%).

^{1}H NMR (d_6-DMSO) 10.8 (broad, 1H), 8.11 (d, 1H), 7.2-7.3 (m, 4H), 7.19 (d, 1H), 3.79 (s, 2H), 2.66 (s, 3H);

MS (ES) $^m/z$ 246 ($[M+H]^+$, 100%), 198 (37%).

(b) 4H-Thieno[2,3-c][1]benzazepin-10-amine maleate

To a pressure bottle was added 10-methylthio-4H-thieno[2,3-c][1]benzazepine hydroiodide (1.22 g, 3.27 mmol) and ammonium acetate (4.50 g) in methanol (15 ml) and the solution was heated at 80 °C for 80 h. The reaction mixture was concentrated, acidified with dilute hydrochloric acid and was washed with diethyl ether. The aqueous phase was basified with dilute aqueous sodium hydroxide and extracted twice with dichloromethane. The dried (magnesium sulfate) organic phases were concentrated to give the free base as a white solid. This was dissolved in 2-propanol (15 ml) and maleic acid (0.44 g) was added. Upon cooling, the solid was collected to give the title compound (0.85 g, 79%) as an off-white solid, m.p. 199.5-200.5 ^{0}C (dec).

Example 3

4,5-Dihydrothieno[3,2-c][1]benzazocin-11-amine

(a) 3-(2-Nitrophenyl)ethenyl-2-thiophenecarbonitrile

To a stirred solution of 3-methyl-2-thiophenecarbonitrile (10.0 g, 20.0 mmol) in N,N-dimethylformamide (60 ml) was added potassium t-butoxide (2.54 g, 20.0 mmol) at 0 ^{0}C. The reaction mixture was stirred for 2 h and then o-nitrobenzaldehyde (2.54 g, 20.0 mmol) was added at 0 ^{0}C and the mixture stirred for 18 h. The mixture was poured into water (500 ml) and the aqueous phase was extracted twice with ethyl acetate. The organic phases were dried (magnesium sulfate) and concentrated to give a crude product. The crude product was purified by column chromatography, using 25% ethyl acetate in hexane as eluent to yield the title compound as an oil which was used without further purification.

(b) 3-(2-Nitrophenyl)ethyl-2-thiophenecarbonitrile

To a stirred solution of 3-(2-nitrophenyl)ethenyl-2-thiophenecarbonitrile (0.5 g, 1.5 mmol) in absolute ethanol (20 ml) was added sequentially $BiCl_3$ (0.5 g, 1.6 mmol) and sodium borohydride (0.6 g, 1.5 mmol); the reaction was then stirred for 6 h. The reaction mixture was poured into water (300 ml) and made acidic with hydrochloric acid. The aqueous phase was extracted twice with ethyl acetate and was dried (magnesium sulfate) and concentrated in vacuo to give the product as an impure oil, which was used without purification in the next step.

(c) 3-(2-Aminophenyl)ethyl-2-thiophenecarbonitrile

The title compound was prepared using the method of Example 4(c).

(d) 4,5-Dihydrothieno[3,2-c][1]benzazocin-11-amine

In a test tube, 3-(2-aminophenyl)ethyl-2-thiophenecarbonitrile hydrochloride (281 mg, 1.06 mmol) was heated at 210-220 °C for 0.5 h. The reaction mixture was partitioned between dichloromethane and dilute aqueous sodium hydroxide. The dried (magnesium sulfate) organic phase was concentrated to give a semi-solid. Column chromatography on silica gel, using 1% methanol in chloroform saturated with ammonia as eluent, then afforded the title compound (0.17 g, 70%) as an off-white solid, m.p. 164-168 ^{0}C.

Example 4

Thieno[2,3-b][1,5]benzothiazepin-4-amine hydrochloride

(a) 2-Mercapto-3-thiophenecarbonitrile

To a solution of 3-thiophenecarbonitrile (18.8 g, 0.172 mol) in anhydrous tetrahydrofuran (175 ml) at -78 °C was added, over 0.5 h, butyllithium (2.5 M in hexanes, 72 ml, 0.18 mol). The solution was stirred for 1 h and was then cannulated into a solution of zinc thiocyanate (31.3 g, 0.172 mol) in anhydrous tetrahydrofuran (175 ml) at -78 °C. After addition was complete, the solution was warmed to 0 °C and stirring was continued for 1 h. To this solution, was added N-chlorosuccinimide (23.0 g, 0.172 mol) in dichloromethane (400 ml). The solution was stirred for 2 h at ambient temperature. The reaction mixture was poured into diethyl ether and extracted twice with dilute sodium hydroxide solution. The dried (magnesium sulfate) organic phase was concentrated to give the crude thiocyanate as an oily solid. This material was taken up in ethanol (200 ml) at 0 °C and sodium borohydride (3.0 g) was added portionwise over 1 h. The solvent was removed in vacuum and the residue was partitioned between diethyl ether and dilute sodium hydroxide solution. The aqueous phase was acidified with dilute hydrochloric acid and the product was extracted twice with diethyl ether. The combined and dried (magnesium sulfate) extracts were concentrated to give the product (13.9 g, 57%) as a black oil which solidified on standing.

^{1}H NMR ($CDCl_3$) 7.66 (d, 1H), 7.28 (d, 1H), 3.6-4.4 (broad, 1H);

MS (CI) $^m/z$ 142 ($[M+H]^+$, 100%).

(b) 2-Nitrophenylthio-3-thiophencarbonitrile

To a stirred solution of 2-mercapto-3-thiophenecarbonitrile (1.00 g, 7.08 mmol) and 2-fluoronitrobenzene (1.00 g, 7.08 mmol) in anhydrous dimethylsulphoxide (10 ml) was added potassium t-butoxide (0.80 g, 7.1 mmol). The solution was then heated at 80 °C for 16 h under nitrogen. The reaction mixture was poured into ethyl acetate and washed thrice with water. The dried (magnesium sulfate) organic phase was concentrated and the residue was purified by column chromatography, using chloroform as eluent, to give crude product (1.0 g). Trituration with 50% diethyl ether in hexanes (5 ml) gave the title compound (0.76 g, 41%) as a yellow solid.

^{1}H NMR (d_6-DMSO) 8.35 (d, 1H), 8.23 (d, 1H), 7.78 (d, 1H), 7.71 (dd, 1H), 7.53 (dd, 1H), 6.92 (d, 1H);

MS (CI) ^{m}/z 263 $[M+H]^+$.

(c) 2-Aminophenylthio-3-thiophenecarbonitrile

2-Nitrophenylthio-3-thiophencarbonitrile (0.74 g, 2.8 mmol) was dissolved in a mixture of methanol (40 ml) and acetic acid (5 ml) and zinc powder (1.0 g) was added portionwise over 0.5 h. The excess zinc was filtered off and the filtrate was concentrated in vacuum. The residue was partitioned between dichloromethane and dilute aqueous ammonium hydroxide. The dried organic phase was concentrated to give a dark oil which partly solidified on standing. This material was purified by chromatography on silica gel using 1% methanol in chloroform saturated with ammonia as eluent, to give the product as an oil.

^{1}H NMR ($CDCl_3$) 7.55 (d, 1H), 7.26 (m, 1H), 7.20 (d, 1H), 7.13 (d, 1H), 6.76 (dd, 2H), 4.43 (broad, 2H);

MS (CI) ^{m}/z 233 ($[M+H]^+$, 100%);

IR (KBr) 2233 cm^{-1} (CN).

(d) Thieno[2,3-b][1,5]benzothiazepin-4-amine hydrochloride

The above oil was immediately converted into the hydrochloride salt by dissolving in 2-propanol and acidifying with hydrochloric acid in 2-propanol. Removal of the solvent gave a solid which was triturated with 2-propanol to give the hydrochloride salt (0.32 g). This salt was heated at 210 - 220 ^{0}C for 10 minutes. Upon cooling the residue was partitioned between dichloromethane and dilute aqueous sodium hydroxide. The dried (magnesium sulfate) organic phase was concentrated in vacuum. The residue was purified by column chromatography, using 1% methanol in chloroform saturated with ammonia as eluent, to give the product (0.19 g) as an oil. This material was taken up in 2-propanol (10 ml) and acidified with hydrogen chloride. The product formed slowly and was collected to give the title compound (0.17 g, 51%) as an off-white solid.

^{1}H NMR (d_6-DMSO) 12.9-13.1 (broad, 1H), 10.0-10.2 (broad, 1H), 9.4-9.6 (broad, 1H), 7.80 (d, 1H), 7.45 (d, 1H), 7.3-7.6 (m, 4 H);

MS (CI) ^{m}/z 233 ($[M+H]^+$, 100%).

Example 5

10H-Thieno[3,2-c][1]benzazepin-4-amine maleate

(a) 2-Methyl-3-thiophenecarbonitrile

To a solution of 3-thiophenecarbonitrile (21.8 g, 0.200 mol) in anhydrous tetrahydrofuran (300 ml) containing diisopropylamine (1 ml) at -78 °C under nitrogen, was added dropwise 2.5 M butyllithium in hexanes (85 ml, 0.21 mol). The solution was stirred for 1 h at that temperature before iodomethane (13 ml, 0.21 mol) was added in a single portion. The reaction mixture was allowed to slowly warm to ambient temperature and was stirred overnight. The reaction mixture was partitioned between ether and water. The dried (magnesium sulfate) organic phase was concentrated to give an oil. Kugelrohr distillation, $b_{2.0\ mm}$ 75-80 °C gave the title compound (21.5 g, 87%) as a colourless liquid.

(b) 2-(4-Methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile

A solution of 2-methyl-3-thiophenecarbonitrile (21.4 g, 0.174 mol) and N-bromosuccinimide (32.4 g, 0.182 mol) with dibenzoylperoxide (0.2 g) in carbon tetrachloride (300 ml) was heated at reflux for 3 h. The solution was cooled to 0 °C and the succinimide was filtered off. The filtrate was washed with water, dried over magnesium sulfate and concentrated in vacuo to afford crude 2-bromomethyl-3-thiophenecarbonitrile as an orange oil. This oil was immediately taken up in 95% ethanol (450 ml) containing sodium p-toluenesulfinate dihydrate (42.8 g, 0.200 mol) and the solution was heated at reflux for 16 h. Whilst still hot, water (300 ml) was added and the reaction mixture was then cooled to 0 °C. The solid was collected, washed successively with 50% aqueous ethanol (150 ml), ether (200 ml) and hexanes (200 ml). After air drying, the title compound (33.9 g, 70%) was obtained as a beige solid, m.p. 174.5-177.5 °C.

(c) 2-((2-Nitrophenyl)(4-methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile

To a solution of 2-(4-methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile (12.0 g, 43.3 mmol) and 2-fluoronitrobenzene (6.72 g, 47.6 mmol) in dimethylsulfoxide (75 ml) was added 25% sodium hydroxide solution (9.0 g). The reaction mixture was stirred for 2.5 h and was then poured into ice/water (1.5 L) and neutralized with ammonium chloride. After sitting overnight the solid was collected, washed with water and air-dried to give the

title compound (14.2 g, 82%) as an impure lilac coloured solid. This material was used without purification.

(d) 2-((2-Aminophenyl)methyl)-3-thiophenecarbonitrile hydrochloride

To a solution of the above material (14.2 g) in methanol (350 ml) and acetic acid (30 ml) was added zinc powder (30 g). The mixture was heated at reflux for 6 h. Upon cooling to room temperature the mixture was filtered and the filtrate was concentrated in vacuo. The residue was partitioned between 3M ammonia and dichloromethane/2-propanol (3:1). The dried (magnesium sulfate) organic phase was concentrated in vacuo to give an oil. This was taken up in ethyl acetate and extracted twice with dilute hydrochloric acid. The aqueous phase was basified with dilute sodium hydroxide and extracted twice with ethyl acetate. The dried (magnesium sulfate) organic phase was concentrated to give a solid. Column chromatography on silica gel, using 2% methanol in chloroform saturated with ammonia as eluent, afforded the title compound. This was immediately taken up in 2-propanol and acidified with hydrogen chloride. Evaporation of the solvent and trituration with ethyl acetate gave the title compound (1.69 g, 15%) as a white solid, m.p. 164-167 ^{0}C. Increasing the eluent to 10% methanol in chloroform saturated with ammonia gave 10H-thieno[3,2-c][1]benzazepin-4-amine (1.66 g, 18%).

(e) 10H-Thieno[3,2-c][1]benzazepin-4-amine maleate

In a test tube, 2-((2-aminophenyl)methyl)-3-thiophenecarbonitrile hydrochloride (1.69 g, 6.74 mmol) was heated at 200 °C for 15 minutes. The compound initially melted and then resolidified. The solid was partitioned between dichloromethane and dilute aqueous sodium hydroxide . The organic phase was dried (magnesium sulfate) and concentrated in vacuo to give 10H-thieno[3,2-c][1]benzazepin-4-amine (1.44 g, 101%) as a grey solid. This material was combined with the material (1.66 g) from step (c) and dissolved in hot 2-propanol (50 ml). Maleic acid (2.0 g) in 2-propanol (15 ml) was added to afford, after filtration, the title compound (4.16 g, 29% total) as an off-white solid, m.p. 222-223 ^{0}C (dec).

Example 6

4H-Thieno[3,2-c][1,6]benzothiazocin-11-amine

(a) 3-Bromomethyl-2-thiophenecarbonitrile

A solution of 2-methyl-2-thiophenecarbonitrile (20.0 g, 0.161 mol), N-bromosuccinimide (32.8 g, 0.185 mol) and dibenzoylperoxide (0.2 g) in carbon tetrachloride (325 ml) was heated at reflux for 4 h. The solution was cooled to 0 °C and the succinimide was removed by filtration. The organic phase was washed with dilute aqueous sodium hydroxide, dried over magnesium sulfate and concentrated in vacuo. Vacuum distillation ($b.p._{1.5\ mm}$ 126-128 ^{0}C) afforded the title compound (15.9 g, 49%) as a colourless oil.

(b) 3-(2-Aminophenylthio)methyl-2-thiophenecarbonitrile hydrochloride

To a degassed solution of 2-mercaptoaniline (2.50 g, 20.0 mmol) in N,N-dimethylformamide (100 ml) was added potassium t-butoxide (2.32 g, 20 .8 mmol). The solution was stirred for 0.25 h and then 3-bromomethyl-2-thiophenecarbonitrile (4.18 g, 20.7 mmol) in N,N-dimethylformamide (10 ml) was added. The solution was stirred for 1 h and then poured onto ice. The aqueous phase was extracted three times with ethyl acetate. The combined organic phases were then washed three times with water. The dried (magnesium sulfate) organic phase was concentrated to give an oil. This was taken up in a 1:1 mixture of diethyl ether and dichloromethane and hydrochloric acid in 2-propanol was added until acidic. The product originally separated as an oil but on stirring overnight crystallized. The solid was collected to give the title compound (3.6 g, 64%) as an off-white solid.

Free base ^{1}H NMR ($CDCl_3$) 7.41 (d, 1H), 7.1-7.2 (m, 2H), 6.91 (d, 1H), 6.71 (d, 1H), 6.59 (t, 1H), 4.2-4.4 (broad, 2H), 4.02 (s, 2H);

MS (CI) ^{m}/z 247 ($[M+H]^+$, 100%).

(c) 4H-Thieno[3,2-c][1,6]benzothiazocin-11-amine

In a test tube, 3-(2-aminophenylthio)methyl-2-thiophenecarbonitrile hydrochloride (1.0 g, 4.06 mmol) was heated at 210-220 ^{0}C for 0.5 h. The reaction mixture was dissolved in methanol (100 ml) and decolourized with charcoal. The solvent was evaporated and the residue partitioned between ethyl acetate and dilute ammonia. The organic phase was dried (magnesium sulfate) and concentrated to give a solid. This was recrystallized from ethyl acetate and cyclohexane to yield the title compound (340 mg), m.p. 166-167 ^{0}C.

Example 7

Thieno[3,2-b][1,5]benzoxazepin-10-amine

(a) 10-Methylthiothieno[3.2-b][1,5]benzoxazepine hydroiodide

A suspension of thieno[3,2-b][1,5]benzoxazepin-10-one (1.07 g, 4.93 mmol) (C. Corral *et al.*, J. Heterocycl. Chem., 1985, **22**, 1349-1352) and Lawesson's reagent (1.86 g) in anhydrous tetrahydrofuran (10 ml) was heated at reflux for 3 h. The solvent was removed in vacuum and the residue was purified by chromatography on silica gel using chloroform as eluent to give the thioamide (0.97 g). This material was immediately taken up in acetone (15 ml) and methyl iodide (2.0 ml) was added and the solution was stirred overnight. The resulting solid was collected to give the title compound (1.27 g, 69%) as a yellow solid.

(b) Thieno[3,2-b][1,5]benzoxazepin-10-amine

A solution of 10-methylthiothieno[3,2-b][1,5]benzoxazepine hydroiodide (0.36 g, 1.00 mmol) in ethanol (10 ml) containing ammonium acetate (0.77 g) was heated at reflux for 15 days. The reaction mixture was poured into dilute hydrochloric acid and was washed with dichloromethane. The aqueous phase was basified with dilute ammonia and extracted twice with dichloromethane. The dried (magnesium sulfate) organic phases were concentrated to give the title compound (40 mg, 11%) as a white solid.

^{1}H NMR ($CDCl_3$) 7.31 (d, 1H), 7.0-7.2 (m, 4H), 6.82 (d, 1H) and 4.6-5.2 (broad, 2H);

MS (CI) $^m/z$ 217 ($[M+H]^+$, 100%).

Example 8

4H-Thieno[2,3-c][1]benzazepin-7,10-diamine

(a) 3-((4-Methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

A solution of 3-methyl-2-thiophenecarbonitrile (20.0 g, 0.161 mol) , N-bromosuccinimide (32.8 g, 0.185 mol) and benzoylperoxide (0.2 g) in carbon tetrachloride (325 ml) was heated at reflux for 4 h. The solution was cooled to 0 °C and the succinimide was removed by filtration. The organic phase was washed with dilute sodium hydroxide solution, dried over magnesium sulfate and concentrated in vacuo. Vacuum distillation, $b_{1.5\,mm}$ 126-8 ^{0}C afforded 3-bromomethyl-2-thiophenecarbonitrile (15.9 g, 49%) as a colourless oil. This

bromomethyl compound (15.9 g, 80 mmol) was taken up in ethanol (200 ml) containing sodium p-toluenesulfinate dihydrate (21.4 g, 100 mmol) and the solution was heated at reflux for 16 h. While still hot , water (150 ml) was added and the reaction mixture was cooled to 0 ^{0}C. The solid was collected, washed successively with 50% aqueous ethanol (100 ml), ether (100 ml) and hexane (100 ml). After air-drying, the title compound (17.2 g, 75%) was obtained as a light tan solid.

(b) 3-((2,4-Dinitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

To a stirred solution of 3-((4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile (2.77 g, 10.0 mmol) in dimethylsulphoxide (50 ml) was added 25% sodium hydroxide (2.88 g). To this was added 2,4-dinitrofluorobenzene (1.4 ml, 11.0 mmol) and the mixture stirred for 0.5 h. The mixture was then poured into water (600 ml). The product was collected to give the title compound (3.5 g) which was used without purification.

(c) 4H-Thieno[2,3-c][1]benzazepin-7,10-diamine

To a stirred suspension of zinc powder (1.4 g, 2.25 mmol) in methanol (20 ml) and acetic acid (1.4 ml) , was added 3-((2,4-dinitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile (1.0 g, 2.25 mmol) and the reaction heated to 80 ^{0}C for 6 h. The mixture was then poured into water (50 ml) and ammonia (50 ml). The aqueous phase was then extracted twice with ethyl acetate and the extracts were dried over magnesium sulfate. Evaporation of the solvent gave a crude product, which was purified by column chromatography, using 5% methanol in chloroform saturated with ammonia as eluent, to give the title compound (200 mg, 39%).

^{1}H NMR (d_6-DMSO) 7.54 (d, 1H), 6.97 (d, 1H), 6.71 (d, 1H), 6.3-6.5 (broad, 2H), 6.20 (s, 1H), 6.16 (d, 1H), 4.6-4.8 (broad, 1H) and 3.49 (s, 2H);

MS (CI) ^{m}/z 230 ($[M+H]^+$, 100%).

Example 9

N-(10-Amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-3-carboximidamide dihydrochloride

To thieno[3,2-b][1,5]benzazepin-7,10-diamine (100 mg, 4.4 mmol) was added S-ethyl-3-thiophenethiocarboximide hydrochloride (110 mg, 5.3 mmol) in 95% ethanol (5 ml) and the solution was stirred for 18 h. The solid was collected and dissolved in hot 95% ethanol acidified with hydrogen chloride. The precipitate was collected to give the title compound (50 mg, 29%) as a white solid.

^{1}H NMR (d_6-DMSO) 13.2 (broad, 1H), 11.6 (broad, 1H), 9.9 (broad, 1H), 9.8 (broad, 1H), 9.3 (broad, 1H), 8.9 (broad, 1H), 8.71 (m, 1H), 8.48 (d, 1H), 7.7-7.9 (m, 2H), 7.57 (d, 1H), 7.40 (s, 1H), 7.38 (d, 1H), 7.34 (d, 1H) and 4.18 (s, 2H);

MS (CI) $^m/z$ 339 ($[M+H]^+$, 65%), 170 (100%).

Example 10

N-(10-Amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-2-carboximidamide dihydrochloride

To thieno[3,2-b][1,5]benzazepin-7,10-diamine (100 mg, 4.4 mmol) was added S-ethyl-2-thiophenethiocarboximide hydrochloride (110 mg, 5.3 mmol) and pyridine hydrochloride (5 mg, 5.6 mmol) in 95% ethanol (5 ml) and the mixture was stirred for 18 h. The title compound was collected as a solid (160 mg, 92%), m.p. 253- 254 ^{0}C.

Example 11

7-Formyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

(a) 4-Dimethoxymethyl-2-nitrofluorobenzene

A solution of 3-nitro-4-fluorobenzaldehyde (8.45 g, 50 mmol) and trimethylorthoformate (7.59 g, 75 mmol) in methanol (20 ml) with p-toluenesulfonic acid (50 mg) was heated at reflux for 18 h. The reaction mixture was made basic with saturated aqueous sodium bicarbonate and the solvent was removed in vacuo. The residue was partitioned between ethyl acetate and water. The dried (magnesium sulfate) organic phase was concentrated to give the title compound (9.11 g, 85%) as a light brown liquid.

(b) 3-((4-Dimethoxymethyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). From 3-(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile (11.6 g, 41.7 mmol) and 4-dimethoxymethyl-2-nitrofluorobenzene (8.98 g, 41.7 mmol) there was obtained the title compound (12.6 g, 64%) as a beige solid, m.p. 132-134 ^{0}C.

(c) 7-Formyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

This compound was prepared similarly to Example 8(c). From 3-((4-dimethoxymethyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile (2.36 g, 5.0 mmol) and zinc powder (2.72 g, 35 mmol) in methanol (50 ml) and acetic acid (7 ml) there was obtained, after treating with aqueous hydrochloric acid in methanol, the title compound (0.34 g, 28%).

MS ^{m}/z 243 $[M+H]^{+}$.

Example 12

7-(1-Azetidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine

A solution of 7-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine (485 mg, 2.00 mmol), azetidine hydrochloride (206 mg, 2.2 mmol) and borane-pyridine complex (0.20 ml, 2.0 mmol) in absolute ethanol (8 ml) was stirred for 16 h. The reaction mixture was concentrated, taken up in ethyl acetate and extracted twice with dilute hydrochloric acid. The aqueous phases were combined, basified with dilute sodium hydroxide and extracted thrice with 5% methanol in chloroform. The dried (magnesium sulfate) organic phase was concentrated to give a beige solid which was triturated with ethyl acetate. The solid was collected to give the title compound (78 mg, 28%) as a beige solid, m.p. 185 ^{0}C (sinters).

Example 13

7-(1-Pyrrolidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine

This compound was prepared similarly to Example 12. Yield 82%; m.p. 210 - 212 ^{0}C.

Example 14

7-(N,N-Diethylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine

(a) 3-((4-(N,N-Diethylaminomethyl)-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). Yield 59%.

(b) 7-(N,N-Diethylamino)methyl-4H-thieno[3,2-b][1,5]benzothiazepin-10-amine

This compound was prepared similarly to Example 8(c). Yield 21%; m.p. 190-191.5 ^{0}C.

Example 15

7-Hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine

To a solution of 7-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine (484 mg, 2.00 mmol) and sodium cyanoborohydride (150 mg, 2.4 mmol) in methanol (4 ml) was added dropwise 4 M hydrochloric acid until the pH of the solution was between 3-4 and the solution was then allowed to stir overnight. The solvent was partitioned between chloroform and water. The dried (magnesium sulfate) organic phase was concentrated to give a solid which was triturated with ethyl acetate to give the title compound (136 mg, 36%). An analytical sample was prepared by HPLC, m.p. 226-228 ^{0}C.

Example 16

Methyl 10-Amino-4H-thieno[2,3-c][1]benzazepin-7-carboxylate

(a) 3-((4-Methoxycarbonyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). Yield 67%.

(b) Methyl 10-amino-4H-thieno[2,3-c][1]benzazepin-7-carboxylate

This compound was prepared similarly to Example 8(c). Yield 10%; m.p. 218-220 ^{0}C.

Example 17

10-Amino-4H-thieno[2,3-c][1]benzazepin-7-carboxamide

(a) 3-((4-Aminocarbonyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). Yield 30%.

(b) 10-Amino-4H-thieno[2,3-c][1]benzazepin-7-carboxamide

This compound was prepared similarly to Example 8(c). Yield 8%; m.p. 224-226 ^{0}C.

Example 18

7-(1-Pyrrolidinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine

(a) 3-((4-(1-Pyrrolidinyl)carbonyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). Yield 90%.

(b) 7-(1-Pyrrolidinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine

This compound was prepared similarly to Example 8(c). Yield 58%; m.p. 229-231 ^{0}C.

Example 19

7-(1-Ethanone)-4H-thieno[2,3-c][1]benzazepin-10-amine maleate

(a) 3-((4-(1-Ethanone)-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b). Yield 73%.

(b) 7-(1-Ethanone)-4H-thieno[2,3-c][1]benzazepin-10-amine maleate

This compound was prepared similarly to Example 8(c). The free base was converted into the maleate salt in 2-propanol.

MS ^{m}/z 257 $[M+H]^{+}$.

Example 20

7-(1-Hydroxyethyl)- 4H-thieno[2,3-c][1]benzazepin-10-amine

This compound was prepared similarly to Example 15. Yield 44%.

MS $^{m}/z$ 259 $[M+H]^{+}$.

Example 21

6-Formyl-4H-thieno[2,3-c][1]benzazepin-10-amine

(a) 5-Dimethoxymethyl-2-nitrofluorobenzene

This compound was prepared similarly to Example 11(a).

(b) 3-((5-Dimethoxymethyl-2-nitrophenyl)(4-methylphenylsulfonyl)methyl)-2-thiophenecarbonitrile

This compound was prepared similarly to Example 8(b).

(c) 6-Formyl-4H-thieno[2,3-c][1]benzazepin-10-amine

This compound was prepared similarly to Example 8(c). Yield 4%; m.p. >230 ^{0}C.

Example 22

Thieno[3,4-b][1,5]benzothiazepin-10-amine maleate

(a) 10-Methylthiothieno[3,4-b][1,5]benzothiazepine hydroiodide

A suspension of thieno[3,4-b][1,5]benzothiazepin-10-one (1.04 g, 4.46 mmol)(J. B. Press *et al.*, J. Org. Chem., 1980, **45**, 497-501) and Lawesson's reagent (1.0 g) in anhydrous tetrahydrofuran (15 ml) was heated at reflux for 4 h. The solvent was removed in vacuum and the residue was purified by chromatography on silica gel using chloroform as eluent to give the crude thioamide. This was immediately taken up in acetone (15 ml) and methyl iodide (2.0 ml) was added and the solution was stirred overnight. The resulting solid was collected to give the title compound (0.68 g, 37%).

^{1}H NMR (d_6-DMSO) 8.07 (d, 1H), 7.68 (d, 1H), 7.3-7.4 (m, 2H), 7.1-7.2 (m, 2H), 6.4 (broad, 1H), 2.54 (s, 3H);

MS (CI) $^m/z$ 264 ($[M+H]^+$, 100%).

(b) Thieno[3,4-b][1,5]benzothiazepin-10-amine maleate

A pressure bottle containing 10-methylthiothieno[3,4-b][1,5]benzothiazepine hydroiodide (676 mg, 1.73 mmol) in methanol (15 ml) and ammonium acetate (2.50 g) was heated at 80 ^{0}C for 120 h. The reaction mixture was filtered and poured into dilute sodium hydroxide solution and extracted twice with dichloromethane. The dried (magnesium sulfate) organic phases were concentrated to give a gummy solid. The product was purified by column chromatography on silica gel using 5% methanol in chloroform saturated with ammonia to give the free base (310 mg, 77%) as an off-white solid. An analytical sample was prepared by dissolving the free base (170 mg) in hot 2-propanol (8 ml) and adding maleic acid (0.10 g). Upon cooling, the solid was collected to give the title compound

(199 mg, 78%) as a white solid, m.p. 220-221 ^{0}C (dec).

Example 23

4-Oxothieno[3,4-b][1,5]benzothiazepin-10-amine

To a suspension of thieno[3,4-b][1,5]benzothiazepin-10-amine (0.13 g, 0.56 mmol) in 50% aqueous methanol (10 ml) was added dilute hydrochloric acid until the solution was acidic. The free base initially dissolved and then precipitated from the solution. To this mixture was added sodium metaperiodate (130 mg, 0.61 mmol). The reaction mixture was stirred for 3 days and then additional sodium metaperiodate (250 mg) was added. The solution was stirred for 3 days. The solution was poured into water, made basic with aqueous sodium carbonate, and extracted twice with 25% methanol in methylene chloride. The dried (magnesium sulfate) organic extracts were combined and evaporated in vacuo to give the crude product (0.09 g). This material was purified by column chromatography on silica gel using 3% methanol in chloroform saturated with ammonia as eluent, to give a

solid. This solid was triturated with methanol, filtered, and washed with ether to give the title compound (44 mg, 31%) as an off-white solid, m.p. 255-257 ^{0}C (dec).

Example 24

10-Oxothieno[3,2-c][1]benzazepin-4-amine maleate

To a solution of 10H-thieno[3,2- c][1]benzazepin-4-amine (2.0 g, 9.33 mmol) in chloroform (200 ml) was added active manganese dioxide (22 g). The solution was heated at reflux for 1.5 h. After cooling to ambient temperature, methanol (50 ml) was added to help dissolve the product. The reaction mixture was filtered, washed with 25% 2-propanol in chloroform (100 ml), and the filtrate was concentrated to give the product (2.11 g, 99%) as a yellow solid. An analytical sample was prepared by dissolving the product (0.46 g, 2.02 mmol) in hot 2-propanol (25 ml) and adding maleic acid (0.3 g) in 2-propanol (10 ml). After cooling, the salt was collected to give the title compound (0.61 g) as a light yellow solid, m.p. 221 - 222 ^{0}C (dec).

Example 25

10-Hydroxy-10H-thieno[3,2-c][1]benzazepin-4-amine maleate

To a solution of 10-oxothieno[3,2-c][1]benzazepin-4-amine (0.54 g, 2.4 mmol) in methanol (25 ml) at 0 ^{0}C was added sodium borohydride (0.15 g, 3.96 mmol). The solution was stirred for 0.5 h and the reaction mixture was then partitioned between methylene chloride and water. The dried (magnesium sulfate) organic phase was concentrated to give a solid. This material was purified by chromatography on silica gel, using 10% methanol in chloroform saturated with ammonia as eluent, to give a beige solid (220 mg, 41%). An analytical sample was prepared by dissolving this material (0.16 g, 2.02 mmol) in hot 2-propanol (25 ml) and adding maleic acid (0.10 g) in 2-propanol (2 ml). After cooling, the salt was collected to give the title compound (0.184 g) as an off-white solid, m.p. 244 -246 ^{0}C (dec).

Example 26

4H-Thieno[2,3-c][1]benzazepin-4,10-diamine dimaleate

To a solution of 4-hydroxy-4H-thieno[2,3-c][1]benzazepin-10-amine (304 mg, 1.32 mmol) in trifluoroacetic acid (4.0 ml) was added, in a single portion, sodium azide (250 mg). The solution was stirred for 0.75 h before diluting with water (50 ml) and methanol (25 ml). To this was added 10% palladium on carbon (50 mg) and the solution was hydrogenated at 35 psi overnight. The reaction mixture was filtered, the filtrate was made basic with dilute sodium hydroxide, and extracted twice with methylene chloride. The dried (magnesium sulfate) organic phase was concentrated to give a solid. This material was taken up in hot 2-propanol (20 ml), filtered, and maleic acid (0.40 g) was added. The resulting solid was collected, washed with 2-propanol and air-dried to give the title compound (428 mg, 70%) as an off-white solid, m.p. 168 - 169 ^{0}C (dec).

Example 27

4-Oxothieno[2,3-c][1]benzazepin-10-amine maleate

To a solution of 4H-thieno[2,3-c][1]benzazepin-10-amine (6.88 g, 32.1 mmol) in chloroform (300 ml) was added activated manganese dioxide (68 g) and the solution was heated at reflux for 2 h. Methanol (100 ml) was added and the solution was filtered. The filtrate was concentrated and the resulting solid was triturated with ether to give the product (7.00 g, 95%) as a yellow solid. An analytical sample was prepared by dissolving the product in hot 2-propanol and adding maleic acid to give the title compound as a pale yellow solid, m.p. 202 - 203 ^{0}C (dec).

Example 28

4-Hydroxy-4H-thieno[2,3-c][1]benzazepin-10-amine maleate

To a solution of 4-oxothieno[2,3-c][1]benzazepin-10-amine (0.50 g, 2.19 mmol) in anhydrous tetrahydrofuran (50 ml) at 0 °C was added dropwise, 1.0 M L-selectride (2.2 ml. 2.2 mmol) in tetrahydrofuran. After addition was complete, the reaction mixture was stirred for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The dried (magnesium sulfate) organic layer was concentrated to give an oil. Column chromatography on silica gel, using 3% methanol in chloroform saturated with ammonia as eluent, gave a cream coloured solid (0.44 g, 88%). This material was taken up in hot 2-propanol (20 ml) and maleic acid (0.32 g) in 2-propanol (10 ml) was added. Upon cooling, the product was collected to give the title compound (0.48 g, 58%) as an off-white solid, m.p. > 250 °C.

Example 29

7-Chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

To a stirred suspension of 7-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine (4.20 g, 17.2 mmol) in methylene chloride (50 ml) was added thionyl chloride (5.36 g, 45.4mmol) dropwise. The reaction mixture was stirred for 1 hour, to this was added ether (50 ml), and the solid was collected by filtration to give 4.6 g (90%) of the title compound as a tan solid, m.p. 273-274 °C.

Example 30

7-(Cyclopropylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine dimaleate

A solution of 7-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride (403 mg, 1.35 mmol) and cyclopropylamine (0.5 ml) in N-methyl pyrrolidinone (5.0 ml) was heated at 50 °C for 18 h. The reaction mixture was poured into water and the resulting solid was filtered off. The filtrate was extracted thrice with ethyl acetate. The combined extracts were washed twice with water and concentrated to give 0.20 g of the product as the free base. An analytical sample was prepared by dissolving the free base in 2-propanol

(10 ml) and maleic acid (0.25 g) was added. The resulting solid was collected to give the title compound (131 mg) as a white solid, m.p. 123-125 ^{0}C (softens).

Example 31

6-Cyano-4H-thieno[2,3-c][1]benzazepin-10-amine fumarate

(a) 3-Fluoro-4-nitrobenzonitrile

To a solution of 3-fluoro-4-nitroaniline (16.8 g, 0.107 mol) (H. H. Hodgson and D. E. Nicholson, J. Chem. Soc., 766 (1941)) in 3M hydrochloric acid (200 ml) at 0 ^{0}C was added dropwise sodium nitrite (8.3 g, 0.12 mol) dissolved in water (100 ml). After addition was complete, the solution was stirred for 0.5 h. The solution was filtered to remove the insoluble material and the filtrate was then added slowly to a solution of potassium cyanide (57.5 g, 0.883 mol) and cuprous oxide (6.0 g, 0.042 mol) in water (270 ml) at 0 ^{0}C. After addition was complete, the solution was stirred for 0.5 h and was then warmed to 30 ^{0}C. Upon cooling the solid was collected and dried. The product was purified by column chromatography on silica gel, using 50% hexane in chloroform as eluent, to give the product (10.9 g, 62%) as a yellow-orange solid, m.p. 72-74 ^{0}C.

(b) 2-((2-Nitro-5-cyanophenyl)(4-methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile

To a solution of 3-fluoro-4-nitrobenzonitrile (10.9 g, 65.6 mmol) and 2-(4-methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile (16.6 g) in dimethylsulfoxide (105 ml) was added 25% sodium hydroxide solution (16.8 g). The reaction mixture was stirred for 6 h and was then poured into ice/water (3 L) and neutralised with acetic acid. After sitting for 1 h, the solid was collected, washed with water, then ether, and air-dried to give the title compound (19.6 g, 77%) as a pale yellow coloured solid, m.p. 209-213 ^{0}C.

(c) 6-Cyano-4H-thieno[2,3-c][1]benzazepin-10-amine fumarate

To a solution of 2-((2-nitro-5-cyanophenyl)(4-methylphenylsulfonyl)methyl)-3-thiophenecarbonitrile (19.6 g, 46.3 mmol) in acetic acid (350 ml) was added zinc powder (27.8 g, 0.425 mol). The reaction mixture was heated at reflux for 1.5 h. The solution was cooled to 10 ^{0}C and the zinc salts were removed by filtration. The filtrate was diluted with 2.5 L of ice water and the solution was neutralised with concentrated ammonia solution. After stirring overnight, the resulting solid was collected, washed with 2 L of water and

then ether (250 ml). After air-drying, the product (9.07 g, 82%) was isolated as a pale yellow solid. An analytical sample was prepared by dissolving the free base (0.452 g) in methanol (10 ml) and fumaric acid (0.232 g) was added. The resulting solid was collected to give the title compound (364 mg) as a pale yellow solid, m.p. 252-253 ^{0}C (dec).

Example 32

6-Aminocarbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine fumarate

To a solution of sulfuric acid (5.0 ml) was added in a single portion 6-cyano-4H-thieno[2,3-c][1]benzazepin-10-amine (415 mg, 1.73 mmol). The solution was stirred overnight and was then poured onto ice. The aqueous mixture was neutralised with aqueous ammonia and the resulting solid was collected The air-dried solid weighed 0.35 g (79%). An analytical sample was prepared by dissolving the free base in methanol (10 ml) and fumaric acid (0.24 g) was added. The resulting solid was collected to give the title compound (235 mg) as a tan solid, m.p. 247-248 ^{0}C (dec).

Example 33

6-Hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine maleate

To a solution of 6-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine (1.14 g, 4.70 mmol) in methanol (15 ml) was added sodium cyanoborohydride (0.45 g). To this solution was added dropwise 4M hydrochloric acid until the pH of the solution was between 3 and 4. The reaction mixture was allowed to stir overnight. The reaction mixture was poured into water and extracted twice with 30% methanol in chloroform. The dried (magnesium sulfate) organic phase was concentrated to give a solid. The sample was purified by column chromatography, using ammoniate 5% methanol in chloroform as eluent to give 1.01 g (88%) of the product as the free base. The free base was dissolved in hot 2-propanol (40 ml) and maleic acid (0.75 g) was added. After stirring overnight, the title compound (0.81 g) was isolated as a tan solid after filtration, m.p. 182-183 ^{0}C (dec).

Example 34

4-Chloro-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

To a solution of 4-hydroxy-4H-thieno[2,3-c][1]benzazepin-10-amine (2.00 g, 8.68 mmol) in methylene chloride (25 ml) was added thionyl chloride (3 ml). The reaction was stirred for 18 h and the reaction mixture was then diluted with ether (25 ml). The solid was collected by filtration, m.p. 275-278 ^{0}C.

Example 35

4-Ethoxy-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

A solution of 4-chloro-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride (100 mg, 0.351 mmol) in absolute ethanol (10 ml) was heated to reflux for 6 h. Upon cooling a solid crystallised out and was collected by filtration to yield the title compound (50 mg, 49%), m.p. 123-125 ^{0}C.

Example 36

6-Aminomethyl-4H-thieno[2,3-c][1]benzazepin-10-amine

To a pressure bottle charged with 6-cyano-4H-thieno[2,3-c][1]benzazepin-10-amine (400 mg, 1.67 mmol) in acetic acid (20 ml) was added Raney Nickel (100 mg). The reaction mixture was hydrogenated at 50 p.s.i. for 12 hours. The catalyst was removed by filtration and the solvent evaporated. To the residue was added water (100 ml) and concentrated ammonium hydroxide (20 ml) and the compound was extracted into chloroform. Evaporation of the solvent gave the title compound (100 mg, 25%), m.p. 183-184 ^{0}C.

Example 37

Ethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate

To a mixture of sulfuric acid (2 ml) and ethanol (2 ml) was added 6-cyano-4H-thieno[2,3-c][1]benzazepin-10-amine (200 mg, 0.836 mmol) and the reaction mixture was heated at reflux for three hours. The reaction was poured into water (200 ml) and made basic with ammonium hydroxide and the solution was extracted with chloroform. Evaporation of the solvent gave crude product. Chromatography on silica gel, using 5% methanol in chloroform saturated with ammonia, gave the title compound (180 mg, 75%), m.p. 222-223 ^{0}C.

Example 38

2-Methylethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate

To 2-propanol (10 ml) at 0 ^{0}C was added diethylamine (0.2 ml, 2 mmol) and sodium cyanide (0.245 g, 5.0 mmol) and the mixture was then stirred for 10 minutes. To this solution was then added 6-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine (0.245 g, 1.0 mmol) and manganese dioxide (1.4 g, 20 mmol) and the reaction stirred for 18 hours. The oxide was removed by filtration and the filtrate was added to water (100 ml) and ammonium hydroxide (20 ml), and then extracted with chloroform. Evaporation of the extracts gave a crude product. Chromatography on silica gel, using 5% methanol in chloroform saturated with ammonia, gave the title compound (80 mg, 27%), m.p. 231-233 ^{0}C.

Example 39

7-(4-Methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine

To a stirred solution of 1-methylpiperazine (22.8 ml, 206 mmol) in 2-propanol (25 ml), cooled to 0 to 5 ^{0}C, was added potassium cyanide (671 mg, 10.3 mmol). After 5 minutes, 7-formyl-4H-thieno[2,3c][1]benzazepin-10-amine (500 mg, 2.1 mmol) was added in one portion, followed by manganese(IV) oxide (4.2 g, 41.3 mmol), added in two portions ten

minutes apart. The reaction was allowed to warm to ambient temperature and stirred overnight. The reaction was filtered and the filtrate was concentrated in vacuo. The crude product was flash chromatographed (silica gel, 10% methanol/chloroform) to yield a yellow solid (220 mg). The solid was recrystallized from hot ethyl acetate/hexane to give the title compound (115 mg, 16%), m.p. 214-216 ^{0}C.

Example 40

6-(4-Methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine

The title compound was prepared using the method of Example 39. Yield 158 mg (23%); m.p. 217-220 ^{0}C.

Example 41

Thieno[2,3b][1,5]benzothiazepin-4,9-diamine maleate

(a) 2,6-Dinitrophenylthio-3-thiophenecarbonitrile

To a stirred solution of 2-mercapto-3-thiophenecarbonitrile (1.4 g, 10 mmol) in N,N-dimethylformamide (25 ml), was added potassium hydroxide (617 mg, 11 mmol), and 2-chloro-1,3-dinitrobenzene (2.0 g, 10 mmol). The resulting mixture was heated at 60 ^{0}C for 16 h. The reaction was concentrated in vacuo, and then partitioned between water and ethyl acetate. The ethyl acetate layer was dried (magnesium sulfate), concentrated in vacuo, then flash chromatographed (silica gel, 25-40% ethyl acetate/hexane) to yield the title compound (400 mg, 13%).

(b) Thieno[2,3b][1,5]benzothiazepin-4,9-diamine maleate

To a stirred solution of 2,6-dinitrophenylthio-3-thiophenecarbonitrile (800 mg) in glacial acetic acid (50 ml), was added in one portion zinc dust (2.5 g, 38.2 mmol). The resulting mixture was heated at reflux for two hours. The reaction was concentrated in vacuo, then partitioned between ethyl acetate and aqueous potassium carbonate. The ethyl acetate layer was dried (magnesium sulfate), concentrated in vacuo, and then flash chromatographed (silica gel, 10% methanol/chloroform) to give the title compound (500

mg, 78%) as a tan solid. An analytical sample was prepared by dissolving this material in hot 2-propanol, and adding maleic acid (1.1 equivalent). The resulting precipitate was dissolved by heating and by the addition of methanol. Upon cooling, the title compound (150 mg) was obtained, m.p. 218-220 ^{0}C (dec).

Example 42

9-Cyano-thieno[2,3b][1,5]benzothiazepin-4-amine

To a solution of sodium nitrite (565 mg, 8.2 mmol) in water (10 ml) cooled to 0 to 5 ^{0}C, was added slowly a suspension of thieno[2,3b][1,5]benzothiazepin-4,9-diamine maleate (2.7 g, 7.4 mmol) in 2N hydrochloric acid (80 ml). The reaction was stirred at 0 to 5 ^{0}C for 30 minutes, then added over several minutes to a solution of potassium cyanide (4.0 g, 62.5 mmol) and copper(I) chloride (2.19 g, 22.2 mmol) in water (50 ml), cooled to 0 to 5 ^{0}C. The reaction was allowed to warm to ambient temperature, then warmed to 60 ^{0}C for 2 h. The reaction was basified with ammonium hydroxide and extracted with ethyl acetate. The ethyl acetate was dried (magnesium sulfate), concentrated in vacuo, and then flash chromatographed (silica gel, 5% methanol/chloroform) to give a solid (190 mg). The solid was triturated with ether and filtered to yield the title compound (90 mg, 5%), m.p. 260-263 ^{0}C.

Example 43

9-Chloro-thieno[2,3b][1,5]benzothiazepin-4-amine

To a solution of sodium nitrite (588 mg, 8.5 mmol) in water (10 ml) cooled to 0 to 5 ^{0}C, was added slowly a suspension of thieno[2,3b][1,5]benzothiazepin-4,9-diamine (1.9 g, 7.7 mmol) in 2N hydrochloric acid (80 ml). The reaction was stirred at 0 to 5 ^{0}C for 30 minutes, then a solution of potassium cyanide (4.16 g, 64 mmol) and copper(I) chloride (2.28 g, 23.1 mmol) in water (50 ml) was added. The reaction was allowed to warm to ambient temperature and then warmed to 60 ^{0}C for 2 h. The reaction was basified with ammonium hydroxide and extracted with ethyl acetate. The extracts were dried

(magnesium sulfate), concentrated in vacuo, and then flash chromatographed (silica gel, 5% methanol/chloroform) to give the title compound (175 mg, 9%), m.p. 225-228 ^{0}C (dec).

Example 44

6-Chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride

To a stirred suspension of 6-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine (2.81 g, 11.5 mmol) in methylene chloride (35 ml) was added thionyl chloride (2.7 ml, 35 mmol) dropwise. The reaction mixture was stirred for 0.33 hour, then ether (100 ml) was added and the solid was collected by filtration to give 3.33 g (97%) of the title compound as a tan solid, m.p. 250 - 253 ^{0}C (dec).

Example 45

7-(4-Carbobenzyloxypiperazinyl)carbonyl-4H-thieno[2,3c][1]benzazepin-10-amine acetate

The title compound was prepared using the method of Example 39. Yield 400 mg (17%), m.p. 162 - 164 ^{0}C.

Example 46

7-[(4-Methylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

To a stirred solution of 7-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride (0.5 g, 1.7 mmol) in N-methylpyrrolidinone (20 ml) containing diisopropylethylamine (0.5 ml) was added 4-methylpiperazine (1.4 g, 16 mmol) and the reaction mixture was stirred at room temperature for 16 h. The solvent was removed using a vacuum pump and the oily residue was triturated with aqueous potassium carbonate solution (100 ml). The solid was collected and recrystallized from ethyl acetate/hexane to afford 220 mg (40%) of the title compound as a colourless solid, m.p. 180 - 181 ^{0}C.

Following the general method of Example 46, the compounds of Examples 47 to 52 were prepared.

Example 47

7-[(4-Morpholinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p. 244 - 245 °C.

Example 48

7-[(N-Methyl-N-propylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p. 152 - 153 °C.

Example 49

7-[(4-(2-Pyridinyl)piperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p. 256 - 257 °C

Example 50

7-[(4-Carbethoxypiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p. 217 - 218 °C.

Example 51

7-[(4-Acetylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p 228 - 229 ^{0}C.

Example 52

7-[N-(2-Fluoroethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

M.p. 180 - 183 ^{0}C.

Example 53

7-[(Methylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

To a pressure bottle charged with 95% ethanol (500 ml) and monomethylamine (40 ml) was added 7-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride (10.0 g, 33.4 mmol). The reaction mixture was stirred for 18 h. The solvent was evaporated, the residue was diluted with dilute aqueous potassium carbonate solution (1000 ml) and the aqueous phase was extracted with methylene chloride. The dried (magnesium sulfate) organic phase was evaporated to yield a crude product, which was crystallized from ethyl acetate to give 8.2 g (95%) of the title compound as an off-white solid, m.p. 264 - 265 ^{0}C.

Example 54

6-[(N,N-Dimethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine

The title compound was prepared similarly to Example 46 using 6-chloromethyl-4H-thieno [2,3-c][1]benzazepin-10-amine hydrochloride. Yield 180 mg (64%), m.p. 205 - 207 ^{0}C.

Example 55

Ethyl 4-amino-10H-thieno[3,2-c][1]benzazepine-7-carboxylate

a) Ethyl 4-((3-cyano-2-thienyl)(4-methylphenyl)sulfonyl)methyl)-3-nitrobenzoate

To a stirred solution of 2-(((4-methylphenyl)sulfonyl)methyl)-3-thiophene carbonitrile (15.3 g, 72.0 mmol) in dimethylsulphoxide (100 ml) was added 25% sodium hydroxide solution (24.0 g). To this mixture was added ethyl 4-fluoro-3-nitrobenzoate (15.3 g, 72.0 mmol) and the reaction mixture was stirred for 2.0 h. The reaction mixture was poured into water (800 ml) and neutralized with acetic acid. The product crystallized and was collected to give the title compound (18.2 g) which was use as is in the next step.

b) Ethyl 4-amino-10H-thieno[3,2-c][1]bezazepine-7-carboxylate maleate.

To a stirred solution of ethyl 4-((3-cyano-2-thienyl)(4-methylphenyl)sulfonyl)methyl)-3-nitrobenzoate (7.5 g, 15.9 mmol) in acetic acid (120 ml) was added zinc (7.3 g, 112 mmol) portionwise. The solution was heated at reflux for 1 h. and then allowed to cool to ambient temperature . The zinc salts were removed by filtration and the filtrate was concentrated in vacuo. The residue was dissolved in 25% methanol in chloroform and this solution was washed twice with 6M aqueous ammonia. The dried organic phase (magnesium sulfate) was evaporated affording the crude product, which was immediately triturated with hot isopropanol (100 ml). Upon cooling, the title compound (4.41 g) was isolated as a white solid, m.p. 222 - 223 ^{0}C.

Example 56

7-Hydroxymethyl-4H-thieno[3,2-c][1]benzazepin-4-amine maleate

To a solution of ethyl 4-amino-10H-thieno[3,2-c][1]bezazepine-7-carboxylate maleate (4.2 g, 14.7 mmol) in anhydrous tetrahydrofuran (150 ml) under nitrogen at 0 ^{0}C was added lithium aluminium hydride (2.23 g, 59 mmol) portionwise. The mixture was allowed to stir for 2 h. The reaction mixture was worked-up by the cautious addition of water (2.3 ml), followed by 15% sodium hydroxide (2.3 ml), and then water (6.7 ml). The aluminium salts were removed by filtration and the filtrate was concentrated to give the crude title compound (3.4 g, 94%). An analytical sample was prepared by dissolving the crude

product (200 mg, 0.82 mmol) in hot 2-propanol (5 ml) and maleic acid (95 mg, 0.82 mmol) was added. The resulting solid was filtered off to give the title compound as a white solid, m.p. 213 - 214 °C.

Example 57

7-(Chloromethyl)-10H-thieno[3,2-c][1]benzazepin-4-amine hydrochloride

The title compound was prepared similarly to Example 44. Yield, 85%, m.p. 272 - 273 °C.

Following the general method of Example 46, the compounds of Examples 58 to 61 were prepared.

Example 58

7-[(Isopropylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine

M.p. 200 - 201 °C.

Example 59

7-[(Ethylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine

M.p. 250 - 251 °C.

Example 60

6-{[(4-Methoxybenzyl)amino]methyl}-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine

Starting with 6-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine hydrochloride; m.p. 174 - 176 °C.

Example 61

[[(10-Amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetonitrile

M.p. 169 - 170 ^{0}C.

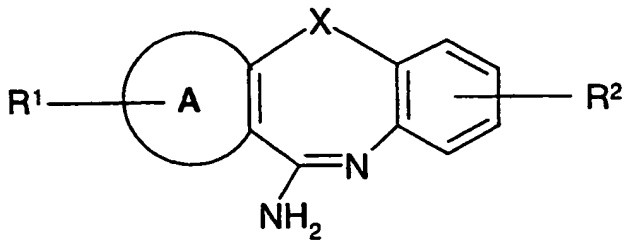
Example 62

2-[[(10-Amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetamide

To 6N sulphuric acid (10 ml) was added [[(10-amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]acetonitrile (0.5 g) and the reaction mixture was warmed to 40 ^{0} C and maintained there for 6 h. The reaction mixture was then cooled to room temperature, poured into water (20 ml) and basified in the cold with aqueous ammonia. The resulting solid was collected, washed with water and air-dried to afford the title compound (180 mg) as a colourless solid, m.p. 141 - 142 ^{0}C

Claims

1. A compound of formula (I)



(I)

wherein:

R^1 represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy or halogen;

R^2 represents hydrogen or a group $-Z-R^3$;

Z represents a bond or C1 to 8 alkyl;

R^3 represents $-OR^4$, $-CH(OR^4)R^{13}$, $-COR^{14}$, $-CO_2R^5$, $-CONR^6R^7$, -CN, halogen, $-NR^8R^9$ or $-NHC(=NH)-R^{10}$;

X represents CH_2, O, $S(O)_m$, CO, $CHOR^{12}$, CH–halogen, $CHNH_2$, $(CH_2)_2$, CH_2O, OCH_2, CH_2S or SCH_2;

m represents an integer 0, 1 or 2;

A represents a heterocyclic ring containing one heteroatom atom selected from O, S and N;

R^4, R^5, R^6, R^7, R^8, R^9 and R^{12} independently represent hydrogen or C1 to 6 alkyl or unsaturated C2 to 6 alkyl; said alkyl or unsaturated alkyl group being optionally further

substituted by one or more groups selected from halogen, –CN, $-CONH_2$ or phenyl; said phenyl being optionally further substituted by C1 to 6 alkyl, C1 to 6 alkoxy or halogen;

R^{10} represents a five membered heterocyclic ring containing one heteroatom selected from O, S and N;

or the groups $-NR^6R^7$ and $-NR^8R^9$ independently represent azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl; said piperazinyl ring being optionally 4-substituted by C1 to 6 alkyl, $-COR^{15}$ or a five or six membered heterocyclic ring containing one heteroatom atom selected from O, S and N; said alkyl group being optionally substituted by phenyl;

R^{13} represents C1 to 6 alkyl;

R^{14} represents hydrogen or C1 to 6 alkyl;

R^{15} represents hydrogen, C1 to 6 alkyl, C1 to 6 alkoxy or phenyl–C1 to 6 alkoxy;

and optical isomers, racemates and tautomers thereof and pharmaceutically acceptable salts thereof.

2. A compound of formula (I), according to Claim 1, wherein X represents CH_2.

3. A compound of formula (I), according to Claim 1, wherein X represents S.

4. A compound of formula (I), according to any one of Claims 1 to 3, wherein $-Z-R^3$ represents $-CH_2-R^3$.

5. A compound of formula (I), according to any one of Claims 1 to 4, wherein A represents a thienyl ring.

6. A compound of formula (I), according to Claim 1, which is:

thieno[3,2-b][1,5]benzothiazepin-10-amine;

4H-thieno[2,3-c][1]benzazepin-10-amine;

4,5-dihydrothieno[3,2-c][1]benzazocin-11-amine;

thieno[2,3-b][1,5]benzothiazepin-4-amine;

10H-thieno[3,2-c][1]benzazepin-4-amine;

4H-thieno[3,2-c][1,6]benzothiazocin-11-amine;

thieno[3,2-b][1,5]benzoxazepin-10-amine;

4H-thieno[2,3-c][1]benzazepin-7,10-diamine;

N-(10-amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-2-carboximidamide;

N-(10-amino-4H-thieno[2,3-c][1]benzazepin-7-yl)thiophen-3-carboximidamide;

7-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-azetidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-pyrrolidinyl)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(N,N-diethylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

methyl 10-amino-4H-thieno[2,3-c][1]benzazepin-7-carboxylate;

10-amino-4H-thieno[2,3-c][1]benzazepin-7-carboxamide;

7-(1-pyrrolidinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-ethanone)-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(1-hydroxyethyl)- 4H-thieno[2,3-c][1]benzazepin-10-amine;

6-formyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

thieno[3,4-b][1,5]benzothiazepin-10-amine;

4-oxothieno[3,4-b][1,5]benzothiazepin-10-amine;

10-oxothieno[3,2-c][1]benzazepin-4-amine;

10-hydroxy-10H-thieno[3,2-c][1]benzazepin-4-amine;

4H-thieno[2,3-c][1]benzazepin-4,10-diamine;

4-oxothieno[2,3-c][1]benzazepin-10-amine;

4-hydroxy-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(cyclopropylamino)methyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-cyano-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-aminocarbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-hydroxymethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

4-chloro-4H-thieno[2,3-c][1]benzazepin-10-amine;

4-ethoxy-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-aminomethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

ethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate;

2-methylethyl 10-amino-4H-thieno[2,3-c][1]benzazepin-6-carboxylate;

7-(4-methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-(4-methylpiperazinyl)carbonyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

thieno[2,3b][1,5]benzothiazepin-4,9-diamine;

9-cyano-thieno[2,3b][1,5]benzothiazepin-4-amine;

9-chloro-thieno[2,3b][1,5]benzothiazepin-4-amine;

6-chloromethyl-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-(4-carbobenzyloxypiperazinyl)carbonyl-4H-thieno[2,3c][1]benzazepin-10-amine;

7-[(4-methylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(4-morpholinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(N-methyl-N-propylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(4-(2-pyridinyl)piperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(4-carbethoxypiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(4-acetylpiperazinyl)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[N-(2-fluoroethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

7-[(methylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

6-[(N,N-dimethylamino)methyl]-4H-thieno[2,3-c][1]benzazepin-10-amine;

ethyl 4-amino-10H-thieno[3,2-c][1]benzazepine-7-carboxylate;

7-hydroxymethyl-4H-thieno[3,2-c][1]benzazepin-4-amine;

7-(chloromethyl)-10H-thieno[3,2-c][1]benzazepin-4-amine;

7-[(isopropylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;

7-[(ethylamino)methyl]-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;

6-{[(4-methoxybenzyl)amino]methyl}-4*H*-thieno[2,3-*c*][1]benzazepin-10-amine;

[[(10-amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetonitrile; or 2-[[(10-amino-4*H*-thieno[2,3-*c*][1]benzazepin-7-yl)methyl](methyl)amino]-acetamide; or an optical isomer, racemate or tautomer of any one thereof or a pharmaceutically acceptable salt of any one thereof.

7. A compound of formula (I), as defined in any one of Claims 1 to 6, for use as a medicament.

8. A pharmaceutical formulation comprising a compound of formula (I), as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof, optionally in admixture with a pharmaceutically acceptable diluent or carrier.

9. A method of treating, or reducing the risk of, a human disease or condition in which inhibition of nitric oxide synthase activity is beneficial which comprises administering to a person suffering from or susceptible to such a disease or condition, a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof.

10. A method of treatment according to Claim 9 in which it is predominantly the neuronal isoform of nitric oxide synthase that is inhibited.

11. A method of treatment according to Claim 9 in which it is predominantly the inducible isoform of nitric oxide synthase that is inhibited.

12. A method of treating, or reducing the risk of, hypoxia or stroke or ischaemia or neurodegenerative conditions or schizophrenia or anxiety or pain or migraine or inflammation, which comprises administering to a person suffering from or susceptible to such a disease or condition a therapeutically effective amount of a compound of formula (I), as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof.

13. A method of treatment according to Claim 12, wherein the condition to be treated is selected from the group consisting of hypoxia, ischaemia, stroke, Parkinson's disease, anxiety, schizophrenia, osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, migraine and pain.

14. A method of treatment according to Claim 13, wherein the condition to be treated is stroke.

15. A method of treatment according to Claim 13, wherein the condition to be treated is pain.

16. A method of treatment according to Claim 13, wherein the condition to be treated is rheumatoid arthritis.

17. A method of treatment according to Claim 13, wherein the condition to be treated is osteoarthritis.

18. A method of treatment according to Claim 13, wherein the condition to be treated is schizophrenia.

19. A method of treatment according to Claim 13, wherein the condition to be treated is Parkinson's disease.

20. A method of treatment according to Claim 13, wherein the condition to be treated is migraine.

21. A method of treating, or reducing the risk of, migraine or other vascular headache which comprises administering to a person suffering from or susceptible to such a disease or condition a therapeutically effective amount of a combination of a compound of formula (I), as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof with a $5HT_{1B/1D}$ agonist or a pharmaceutically acceptable salt thereof.

22. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of human diseases or conditions in which inhibition of nitric oxide synthase activity is beneficial.

23. The use as claimed in Claim 22 wherein it is predominantly the neuronal isoform of nitric oxide synthase that is inhibited.

24. The use as claimed in Claim 22 wherein it is predominantly the inducible isoform of nitric oxide synthase that is inhibited.

25. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of hypoxia or stroke or ischaemia or neurodegenerative conditions or schizophrenia or anxiety or pain or migraine or inflammation.

26. The use as claimed in Claim 25, wherein the condition is selected from the group consisting of hypoxia, ischaemia, stroke, Parkinson's disease, anxiety, schizophrenia, osteoarthritis, rheumatoid arthritis, inflammatory bowel disease, migraine and pain.

27. The use as claimed in Claim 26, wherein the condition is stroke.

28. The use as claimed in Claim 26, wherein the condition is pain.

29. The use as claimed in Claim 26, wherein the condition is rheumatoid arthritis.

30. The use as claimed in Claim 26, wherein the condition is osteoarthritis.

31. The use as claimed in Claim 26, wherein the condition is schizophrenia.

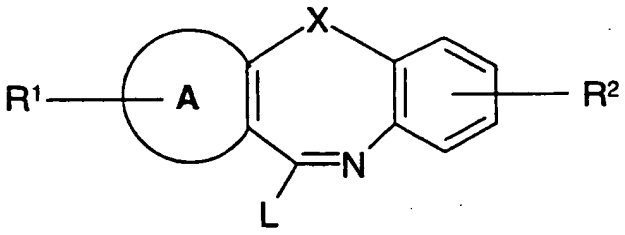
32. The use as claimed in Claim 26, wherein the condition is Parkinson's disease.

33. The use as claimed in Claim 26, wherein the condition is migraine.

34. The use of a compound of formula (I) as defined in any one of Claims 1 to 6, or an optical isomer, racemate or tautomer thereof or a pharmaceutically acceptable salt thereof in combination with a $5HT_{1B/1D}$ agonist or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment or prophylaxis of migraine or other vascular headache.

35. A process for the preparation of a compound of formula (I), as defined in any one of Claims 1 to 6, and optical isomers, racemates and tautomers thereof and pharmaceutically acceptable salts thereof, which comprises:

(a) preparing a compound of formula (I) by reacting a corresponding compound of formula (II)

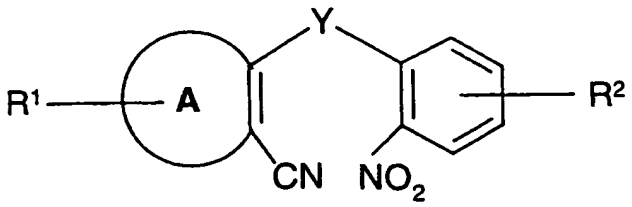


(II)

wherein R^1, R^2, A and X are as defined in Claim 1 and L is a leaving group,

with a source of $-NH_2$ such as ammonia or ammonium acetate;

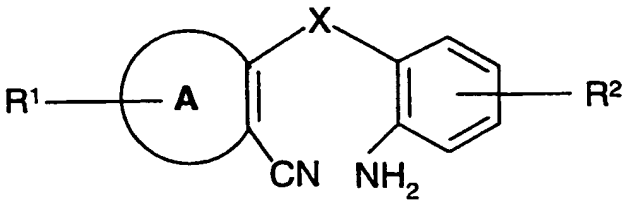
(b) preparing a compound of formula (I) by reduction and cyclisation of a corresponding compound of formula (III)



(III)

wherein R^1, R^2 and A are as defined in Claim 1, and Y represents X (which is as defined above) or $CHSO_2C_6H_4CH_3$;

(c) preparing a compound of formula (I) by cyclisation of a corresponding compound of formula (IV)



(IV)

wherein R^1, R^2, A and X are as defined in Claim 1;

(d) preparing a compound of formula (I) wherein R^2 represents $-Z-CH_2-NR^8R^9$ by reductive amination of a corresponding compound of formula (I) wherein R^2 represents -Z-CHO;

(e) preparing a compound of formula (I) wherein R^2 represents $-Z-NR^8R^9$ by amination of a corresponding compound of formula (I) wherein R^2 represents $-Z-L'$ and L' is a leaving group;

(f) preparing a compound of formula (I) wherein X represents C=O by oxidation of a corresponding compound of formula (I) wherein X represents CH_2;

(g) preparing a compound of formula (I) wherein X represents CHOH by reduction of a corresponding compound of formula (I) wherein X represents C=O;

(h) preparing a compound of formula (I) wherein X represents $CHNH_2$ by converting a compound of formula (I) wherein X represents CHOH into the corresponding azide wherein X represents CHN_3, followed by reduction;

(i) preparing a compound of formula (I) wherein X represents $S(O)_m$ and m represents 1 or 2, by oxidation of a corresponding compound wherein X represents $S(O)_m$ and m represents 0;

(j) preparing a compound of formula (I) wherein R^2 represents $-Z-CONR^6R^7$ or $-Z-CO_2R^5$ by oxidation of the corresponding compound wherein R^2 represents $-Z-CHO$;

(k) preparing a compound of formula (I) wherein R^2 represents $-Z-CONH_2$ or $-Z-CO_2R^5$ by solvolysis of the corresponding compound wherein R^2 represents $-Z-CN$;

or

(l) preparing a compound of formula (I) wherein X represents $CHOR^{12}$ by solvolysis of the corresponding compound wherein X represents CH–halogen;

and where necessary converting the resultant compound of formula (I), or another salt thereof, into a pharmaceutically acceptable salt thereof, or vice versa, and where desired converting the resultant compound of formula (I) into an optical isomer thereof.

INTERNATIONAL SEARCH REPORT

International application No.
P../SE 00/01034

A. CLASSIFICATION OF SUBJECT MATTER
IPC7: C07D 495/04, C07D 498/04, C07D 233/20, A61K 31/55, A61K 31/395, A61K 31/553, A61K 31/554, A61P 9/00, A61P 19/00, A61P 25/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9717344 A1 (ASTRA AKTIEBOLAG), 15 May 1997 (15.05.97) --	1-35
A	US 5605897 A (CHARLES M. BEASLEY JR. ET AL), 25 February 1997 (25.02.97) --	1-35
A	CH 476753 A (DR. A. WANDER AG.), 30 Sept 1969 (30.09.69) -- --------	1-35

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 October 2000	18 -10- 2000
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anna Sjölund/GH Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/SE00/01034

Box I **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9-21
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet *

2. ☒ Claims Nos.: 22-24
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see next sheet **

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

Box II **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/01034

*

Claims 9 - 21 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/ Rule. 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

**

The expression "inhibition of nitric oxide synthase activity is beneficial" is not clear and concise. The claims 22-24 therefore do not comply with the requirements in PCT Article 6.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 00/01034

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9717344 A1	15/05/97	AU 701329 B	28/01/99
		AU 4960896 A	23/09/96
		AU 7592796 A	29/05/97
		BR 9611276 A	26/01/99
		CZ 9801392 A	16/09/98
		EP 0820226 A	28/01/98
		EP 0861250 A	02/09/98
		HU 9900142 A	28/05/99
		IL 124296 D	00/00/00
		JP 2000500132 T	11/01/00
		NO 982072 A	03/07/98
		PL 326554 A	28/09/98
		SE 9600275 D	00/00/00
		SK 61098 A	11/01/99
		SE 9603300 D	00/00/00
		SE 9603301 D	00/00/00
US 5605897 A	25/02/97	US 5627178 A	06/05/97
		US 5817655 A	06/10/98
		US 5817656 A	06/10/98
		US 5817657 A	06/10/98
		US 6008216 A	28/12/99
		US 5229382 A	20/07/93
CH 476753 A	30/09/69	DE 1470416 A	14/05/69
		DE 1620711 A	04/06/70
		DE 1620712 A	04/06/70
		DE 1620713 A	02/07/70
		NL 147426 B	15/10/75
		SE 336800 B	19/07/71